



ENHANCING POST-MARKET EVIDENCE GENERATION FOR MEDICAL PRODUCTS

The Medical Product Evidence Generation Framework project, organized by the Reagan-Udall Foundation for the FDA, consisted of a series of roundtable meetings and listening sessions to inform the development of a framework to facilitate post-market medical product research integrated into clinical care. Specifically, this report addresses actions that should be taken to help close gaps in clinical evidence to inform patient care and, when appropriate, to capture data of sufficient quality to support regulatory decision-making regarding medical product claims.

The Medical Product Evidence Generation Framework project was led by an Expert Panel that drafted recommendations for the FDA and other stakeholders on how to encourage and support evidence generation in the course of routine care delivery. Expert panel members include:

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Table of Contents

Glossary.....	4
I. Introduction.....	8
II. Background.....	12
III. Methodology and Stakeholder Input.....	17
IV. Recommendations.....	20
V. Conclusion.....	38
Appendix A: Panelist Biographies.....	41
Appendix B: Evidence Generation Roundtables.....	46
Appendix C: Roundtable Participants.....	48
Appendix D: Listening Sessions.....	50
Appendix E: Use Cases.....	52
Appendix F: Stakeholder Responsibilities for Implementation.....	55

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of \$399,966 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit [FDA.gov](https://www.fda.gov).

Term	Abbreviation	Definition
Accelerated approval		Accelerated approval allows for earlier access to drugs and biologics based on initial evidence of safety and effectiveness while the confirmatory studies required to verify clinical benefit are being conducted
Advanced Research Projects Agency for Health	ARPA-H	A research funding agency that supports transformative biomedical and health breakthroughs
Adverse event	AE	Any undesirable experience associated with the use of a medical product in a patient
Affordable Care Act	ACA	The Patient Protection and Affordable Care Act, referred to as the Affordable Care Act or "ACA" for short, is the comprehensive health care reform law enacted in March 2010
Centers for Disease Control and Prevention	CDC	The national public health agency of the United States. It is a United States federal agency under the Department of Health and Human Services
Centers for Medicare and Medicaid Services	CMS	A federal agency within the United States Department of Health and Human Services (HHS) that administers the Medicare program and works in partnership with state governments to administer Medicaid, the Children's Health Insurance Program (CHIP), and health insurance portability standards
Clinical Data Interchange Standards Consortium	CDISC	CDISC ODM is a vendor-neutral, platform-independent format. It supports the electronic acquisition, exchange, and archival of clinical trial data for the medical and biopharmaceutical industries
Comparative Clinical Effectiveness Research	CER	CER compares the effectiveness of two or more interventions or approaches to health care, examining their risks and benefits
Claims data		An electronic record about medical appointments and billing and insurance information; includes medical claims, pharmacy claims, dental claims
Current Procedural Terminology®	CPT	CPT codes offer a uniform language for coding medical services and procedures to streamline reporting
Decentralized Clinical Trial	DCT	Some or all of a clinical trial's activities that occur at locations other than a traditional clinical trial site
Electronic Health Record	EHR	A digital version of a patient's paper chart
Federally Qualified Health Center	FQHC	Federally funded nonprofit health centers or clinics that serve medically underserved areas and populations

Term	Abbreviation	Definition
Fit-for-Purpose	FFP	The level of validation is sufficient to support its context of use.
Health care System		An organization of people, institutions, and resources that delivers health care services to meet the health needs of target populations; sites include, but are not limited to, hospitals, clinics, FQHCs, pharmacies, and people's homes
Information Technology	IT	The use of computer systems or devices to access information
Institutional Review Board	IRB	An IRB is group that has been formally designated to review and monitor biomedical research involving human subjects
International Classification of Diseases	ICD	ICD-10 is a classification system of diagnosis codes
The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use	ICH	ICH brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines
Label		The FDA-approved label is the official description of a drug product which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside drug product packaging
Marketing Status		Marketing status indicates how a drug product is sold in the United States. Drug products in Drugs@FDA are identified as follows: prescription, over-the-counter, discontinued, and non-drug products that have been tentatively approved.
Minimum Clinical Oncology Data Elements	mCODE	The goal of mCODE is to define a foundational set of critical data elements to enable clinical care and research via the EHR.
National Cancer Institute	NCI	Coordinates the United States National Cancer Program and is part of the National Institutes of Health, which is one of 11 agencies that are part of the U.S. Department of Health and Human Services.
National Institutes of Health	NIH	The primary agency of the United States government responsible for biomedical and public health research

Term	Abbreviation	Definition
National Patient-Centered Clinical Research Network	PCORnet	A national resource, funded by Patient-Centered Outcomes Research Institute (PCORI), where high quality health data, patient partnership, and research expertise deliver fast, trustworthy answers that advance health outcomes
Nurse practitioner	NP	A nurse who has advanced clinical education and training; they perform physical exams, diagnose and treat diseases and other health conditions, and prescribe medication
Office for Human Research Protections	OHRP	Provides leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS)
Office of the National Coordinator for Health Information	ONC	The principal federal entity charged with coordination of nationwide efforts to implement and use the most advanced health information technology and the electronic exchange of health information
Oncology Center of Excellence	OCE	Facilitates the development and clinical review of oncology products by uniting scientific experts across the FDA's product centers to conduct expedited review of drugs, biologics, and devices
Patient-Centered Outcomes Research Institute	PCORI	An independent, nonprofit research organization that seeks to empower patients and others with actionable information about their health and health care choices
Patient-participant		A person participating in a research study
Physician	MD, DO	A medical doctor (MD) or doctor of osteopathic medicine (DO)
Physician assistant	PA	A licensed medical professional who holds an advanced degree and provides direct patient care
Point-of-Care	POC	Health care services delivered in the most appropriate and convenient location for the patient
Point-of-Care Trial	POC Trial	Point-of-care clinical trials are designed to integrate clinical research and routine care delivery
Post-market		After a product's initial market authorization; activities or studies conducted after approval or clearance of a medical product; a medical product with approval or clearance for at least one indication
Post-marketing Commitments	PMCs	Studies or clinical trials that a sponsor has agreed to conduct, but that are not required by a statute or regulation
Post-marketing Requirements	PMRs	Include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations
Pragmatic Evidence Generation		Evidence generated by pragmatic trials
Pragmatic Trial		Studies designed to test the effectiveness of the intervention in broad routine clinical practice
Pre-approval		Phase 1-3 clinical trials; a medical product not yet been deemed safe and effective by the FDA for a specific indication

Term	Abbreviation	Definition
Project Pragmatica		An Oncology Center of Excellence (OCE) project that seeks to introduce functional efficiencies and enhance patient centricity by integrating aspects of clinical trials with real-world routine clinical practice through appropriate use of pragmatic design elements
Quality by Design	QbD	A systematic approach to pharmaceutical development that begins with predefined objectives
Randomised Evaluation of COVID-19 Therapy trial	RECOVERY	A multi-center randomized control trial with an adaptive platform design based in the United Kingdom
Real-world data	RWD	Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources; examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status
Real-world evidence	RWE	The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD
Relative value unit	RVU	RVUs are calculated from three components: work, practice expense, and malpractice. The work RVU, or wRVU, measures the time, effort, and skill required for a service or procedure
Serious adverse event	SAE	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
U.S. Department of Health and Human Services	HHS	The mission of HHS is to enhance the health and well-being of all Americans, by providing for effective health and human services and by fostering sound, sustained advances in the sciences underlying medicine, public health, and social services.
U.S. Food and Drug Administration	FDA	The FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.
Use case		A scenario of steps the user takes to interact with a system; use cases describe the system functions from the perspective of the end user

Pragmatic Evidence Generation to Support Regulatory Decision-Making

I. INTRODUCTION

The U.S. Food and Drug Administration (FDA) is an essential agency for protecting public health by assuring the safety, efficacy, and security of medical products and devices for human use. Their application of rigorous standards for clinical trial design, focus on clinically meaningful endpoints and assurance of study integrity and data quality, along with a workforce comprised of outstanding scientists and clinicians, has led to recognition of the FDA as the global leader in managing a regulatory system for the review of medical products. The system for initial review of marketing applications, while sometimes difficult to understand and navigate, generally works well for delivering safe and effective medical products to the public in a timely fashion.

However, gaps, often identified in the clinical practice guidelines issued by medical professional societies, remain in the clinical evidence base for many products because the populations with the greatest disease burdens are often underrepresented in clinical trials or because trials to support initial marketing applications focus on very narrow potential indications. While recent FDA initiatives to require diversity plans seek to remedy this problem, continued generation of high-quality evidence about medical products throughout their life cycle is essential to ensure their safe and appropriate use among all populations for which the treatment is intended. A system that fosters post-market evidence generation as part of health care delivery is also important to identify rare or delayed safety signals, to develop information about the relative effectiveness of a product compared to products with similar indications, and to identify new potential uses of products that may broaden their impact on population health. The current system used to generate evidence in support of initial marketing applications is complex, expensive, time-consuming and may not be necessary to deliver the information needed to close evidence gaps in clinical practice or to optimize the use of products already shown to be safe and effective.

Instead, development of a pragmatic evidence generation framework that leverages the U.S. health care system¹ to resolve clinically meaningful evidence gaps for medical

¹ An organization of people, institutions, and resources that delivers health care services to meet the health needs of target populations; sites include, but are not limited to, hospitals, clinics, FQHCs, pharmacies, and people's homes (see glossary)

products (i.e., drugs, devices, and biologics) and supports regulatory submissions for new indications or other revisions to labeling, has the potential to greatly accelerate learning about medical products in the post-market setting. Ideally, the framework would support evidence generation that impacts clinical practice more quickly and efficiently than that provided by the current clinical research ecosystem. However, the success of such an approach hinges on overcoming barriers addressed throughout this document. Improving the evidence generation process through greater clinician engagement, broader patient participation, design of pragmatic clinical studies, and collection of routine clinical data within the context of health care delivery is of interest not only to the FDA, but also to other Federal agencies, as well as health systems, health insurers, sponsors, clinicians, and patients.

This report addresses barriers, proposes solutions, and makes recommendations to the FDA and other stakeholders that aim to facilitate evidence generation in the post-market setting. For the purposes of this document, ***pragmatic evidence generation refers to conducting prospective clinical (preferably randomized) studies of medical products already on the market for at least one indication (post-market).***²

Pragmatic evidence generation studies conducted in the post-market setting involve products where the risks of a product are generally known and benefits have been established for at least one indication, with the goal to expand to another indication or patient population, assess comparative effectiveness with other medical products, comply with a post-market regulatory requirement, and/or meet another regulatory, clinical practice, or reimbursement purpose. Pragmatic evidence generation can include, but is not limited to, randomized studies conducted in the context and flow of routine care, including community settings.

The pragmatic evidence generation framework described herein will generally NOT be applicable to pre-approval clinical trials (e.g., phases 1-3) of new drugs, confirmatory trials following accelerated approval, or retrospective analyses of real-world data (RWD), although specific recommendations might be relevant to such studies depending on the research context and study objectives. Furthermore, all of the recommendations herein must be considered within the FDA's overarching mandate to determine if medical products are safe and effective to use for specific purposes in specific populations; it is recognized that not all recommendations will be applicable to all post-

² For purposes of this document, post-market refers to a medical product with approval or clearance for at least one indication (see glossary for additional description)

market studies. However, the pragmatic evidence generation framework envisioned, if implemented with the support of the FDA, health systems, payers, clinicians, and patients/families, has the potential to simplify and accelerate post-market evidence generation and to begin to realize the vision of the learning health care system.³

System-level and cultural barriers exist that prevent sponsors, investigators, clinicians, and care teams from routinely engaging in evidence generation. A pragmatic evidence generation system requires health systems, sponsors, administrative/regulatory systems (e.g., institutional review boards (IRBs), contracting offices), funding entities, payers, and the FDA to:

- ▶ Design pragmatic, resource-efficient studies that resolve evidence gaps and generate clinically meaningful results that impact clinical practice;
- ▶ Streamline data collection as much as possible while ensuring that data quality and completeness is acceptable for regulatory purposes;
- ▶ Provide opportunities and incentives to the entire patient care team to engage in pragmatic evidence generation, while reducing the administrative and regulatory requirements typically in place for clinical trials;
- ▶ Prioritize studies based on public health needs and gaps in clinical evidence, creating a roadmap for the FDA, sponsors, and the research community to follow; and
- ▶ Engage relevant stakeholders to address who decides on the priorities for knowledge generation including the following: what studies will be conducted; how the work is funded; how clinicians and sites are identified to participate; how information is gathered and analyzed; and the degree to which elements of the health care system and payers are expected to participate and how they are encouraged, incentivized, or required to participate; and how study results may be shared back to the stakeholder community to impact health care delivery.

Implementation of an effective post-market pragmatic evidence generation framework requires the creation of a new paradigm that enables continued learning about the safety and effectiveness of medical products once introduced into clinical practice. Such a paradigm is very different from the current “industry-sponsored” FDA approval-oriented model used to achieve initial marketing approval for medical products and requires leadership beyond the boundaries of the FDA. While it shares many features of pre-approval research (e.g., specification of objectives/endpoints, randomization,

³ Greene SM, Embi P, Gaines M, et. al., Editors. 2021. *Priorities on the Health Horizon: Informing PCORI's Strategic Plan*. NAM Special Publication. Washington, DC: National Academy of Medicine.

data collection and analysis), the underlying business dynamic to support post-market evidence generation is unlike “approval-oriented” studies with a stronger focus on knowledge generation to improve health outcomes in real-world populations. Garnering financial support for such studies can be challenging because the return on investment may be less immediate or tangible. This new paradigm requires different assumptions about how priorities are established, how different segments of the health care ecosystem will be expected to provide support, and how providers will be expected to participate. The paradigm should be grounded in the expectation that all components of the health care ecosystem have an obligation to generate new knowledge that improves clinical care or public health and will benefit the whole system by doing so. As such, all participants in health care delivery should be encouraged to be engaged in pragmatic evidence generation either by provision of funding and/or research infrastructure or by participating as providers.

Part of FDA’s mission is advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable.⁴ The objective of this report is to provide recommendations for changes that can be made by FDA and other stakeholders to facilitate and support post-market pragmatic evidence generation studies – studies that answer clinically meaningful questions and address gaps in clinical evidence that directly impact how care is managed in the U.S. – in a timely manner and with data of sufficient quality to enable regulatory decisions. Such changes will rely on the involvement of **ALL** stakeholders, with the FDA serving as a catalyst for innovation in the post-market evidence generation ecosystem.

⁴ FDA. What We Do. FDA.gov . Published March 28, 2018. <https://www.fda.gov/about-fda/what-we-do>

II. BACKGROUND

FDA Commissioner Dr. Robert M. Califf has called for “a major reformation of our national system for generating medical evidence... to facilitate the translation of biomedical research into useful products and interventions.”⁵ The current clinical trial system is inefficient, slow, and expensive, and engages a small segment of the population.⁶ As clinical trials become more complex, user friendliness declines for all involved – researchers, clinicians, and patient-participants. Clinical trials conducted in research facilities fail to mirror the diversity and heterogeneity that exists within the wide array of clinical practice settings across the U.S.⁷

Clinical trials have been separated from patient care, with expansive treatment protocols, extensive data collection requirements, and well-intentioned regulatory requirements that make them very expensive to conduct and difficult for clinicians and their patients to participate.⁸ Barriers also exist to conducting trials with interventions that have little or no commercial support, such as those involving generic drugs.⁹ Factors contributing to the expense and inefficiency of clinical trials are listed in Table 1.

Often, incentives (e.g., financial incentives, academic advancement) driving research are not patient- or care-centered and trial results do not inform practice decisions.¹⁰ Moreover, a small proportion of studies actually provide clinically relevant outcomes. Many trials are underpowered and not well designed to answer key questions.¹¹ For example, of the 2,895 trial arms studying COVID-19 therapeutics, identified through ClinicalTrials.gov and the World Health Organization (WHO) clinical trial registry, only ~5% were randomized and adequately powered to enable the generation of definitive results about treatment efficacy.¹²

⁵ Califf RM. Now is the time to fix the evidence generation system. *Clinical Trials*. 2023;20(1):174077452211476. doi:<https://doi.org/10.1177/17407745221147689>

⁶ Bowman L, Weidinger F, Albert MA, et al. Randomized trials fit for the 21st century. A joint opinion from the European Society of Cardiology, American Heart Association, American College of Cardiology, and the World Heart Federation. *European Heart Journal*. 2022;44. doi:<https://doi.org/10.1093/eurheartj/ehac633>

⁷ Ford I, Norrie J. The Changing Face of Clinical Trials: Pragmatic Trials. *New England Journal of Medicine*. 2016;375(5):454-463. doi:<https://doi.org/10.1056/nejmra1510059>

⁸ Coalition for Advancing Clinical Trials at the Point of Care. Advancing Clinical Trials at the Point-of-Care: Building a Platform to Give Patients and Clinicians Needed Evidence for Better Care. *actpoc.org*. Published November 9, 2021. Accessed August 23, 2023. <https://actpoc.org/updates/letter-from-the-coalition/11-9-2021>

⁹ Bowman L, Weidinger F, Albert MA, et al. Randomized trials fit for the 21st century. A joint opinion from the European Society of Cardiology, American Heart Association, American College of Cardiology, and the World Heart Federation. *European Heart Journal*. 2022;44. doi:<https://doi.org/10.1093/eurheartj/ehac633>

¹⁰ Ford I, Norrie J. The Changing Face of Clinical Trials: Pragmatic Trials. *New England Journal of Medicine*. 2016;375(5):454-463. doi:<https://doi.org/10.1056/nejmra1510059>

¹¹ Advancing Clinical Trials at the Point of Care (ACT@POC). Closing Evidence Gaps By Integrating Research and Care Delivery. <https://actpoc.org/>

¹² Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. *Nature Reviews Drug Discovery*. 2021;20(4):254-255. doi:10.1038/d41573-021-00037-3

Table 1: Factors Contributing to the Expense and Inefficiency of Clinical Trials ^{13,14,15}

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- ▶ Complex protocols
 - ▶ Sample sizes often not powered to provide results applicable to real-time patient care
 - ▶ Uncertain results/large amount of noise from underpowered trials
 - ▶ Conducted in research centers parallel to clinical care systems
 - ▶ Extensive data collection requirements
 - ▶ Long and complex case report forms
 - ▶ Stringent eligibility criteria that limit recruitment and retention
 - ▶ Lack of diversity of study populations/not representative of the general population
 - ▶ Long and complex consent forms
 - ▶ Staying current with technology and innovation
 - ▶ Time-consuming and complex regulatory requirements
 - ▶ Minimal financial support for treatments using generic drugs
-

Patient-participants are often not representative of clinical practices across the U.S. A cross-sectional study assessing factors associated with invitations to participate in clinical trials reported that only 9% of adults were invited to participate.¹⁶ A survey by the PAN Foundation reported that 78% of adults with chronic illnesses have never discussed participating in a clinical trial with a health care provider.¹⁷ In 2020, although over 40% of the U.S. population identified as non-White, only 25% of participants in the clinical trials of the 53 novel drugs approved by the FDA in the same year were non-White.^{18,19} External validity of clinical trial results is a long-standing problem that the FDA has now begun to address by requiring that sponsors submit plans for enrolling representative patient populations in clinical trials.

To guide funding of patient-centered comparative clinical effectiveness research (CER) and other initiatives, the Patient-Centered Outcomes Research Institute (PCORI) published five priorities for health (Table 2).²⁰ In order to achieve these five priorities, significant changes are needed in how post-market clinical research is conducted. Traditional randomized clinical trials, with the complexities identified above, will need to be simplified in their design and conduct to meet these goals. Methods will need to be established to rapidly disseminate new findings to payers and clinicians to secure reimbursement and stimulate use in practice.

¹³ Califf RM. Now is the time to fix the evidence generation system. *Clinical Trials*. 2023;20(1):174077452211476. doi:<https://doi.org/10.1177/17407745221147689>

¹⁴ Coalition for Advancing Clinical Trials at the Point of Care. *Advancing Clinical Trials at the Point of Care (ACT@POC)*. Margolis Center for Health Policy. Published November 9, 2021. Accessed August 23, 2023. <https://healthpolicy.duke.edu/publications/advancing-clinical-trials-point-care-actpoc#:~:text=%E2%80%9CThrough%20its%20more%20accessible%2C%20cost>

¹⁵ Horby P, Mullard A. RECOVERY 1 Year on: a Rare Success in the COVID-19 Clinical Trial Landscape. *Nature Reviews*. 2021;20:336-337. Accessed August 9, 2023. www.nature.com/nrd

¹⁶ Williams CP, Senft Everson N, Shelburne N, Norton WE. Demographic and Health Behavior Factors Associated With Clinical Trial Invitation and Participation in the United States. *JAMA Netw Open*. 2021 Sep 1;4(9):e2127792. doi: 10.1001/jamanetworkopen.2021.27792.

¹⁷ PAN Foundation. Clinical trial awareness and participation Survey research results. PAN Foundation. Published January 2023. Accessed August 9, 2023. <https://www.panfoundation.org/national-poll-adults-have-high-interest-in-clinical-trials-but-lack-information/>

¹⁸ US Census Bureau. 2020 U.S. Population More Racially and Ethnically Diverse than Measured in 2010. The United States Census Bureau. Published 2021. <https://www.census.gov/library/stories/2021/08/2020-united-states-population-more-racially-ethnically-diverse-than-2010.html>

¹⁹ US Food and Drug Administration. 2020 drug trials snapshot. Summary report. <https://www.fda.gov/media/145718/download> (accessed September 12, 2023).

²⁰ Greene SM, Embi P, Gaines M, et. al., Editors. 2021. *Priorities on the Health Horizon: Informing PCORI's Strategic Plan*. NAM Special Publication. Washington, DC:National Academy of Medicine.

Table 2: PCORI's Adopted National Priorities for Health

1. Increase evidence for existing interventions and emerging innovations in health
2. Enhance infrastructure to accelerate patient-centered outcomes research
3. Advance the science of dissemination, implementation, and health communication
4. Achieve health equity
5. Accelerate progress toward an integrated learning health system

Post-market studies may be conducted using pragmatic/Point of Care (POC) or decentralized clinical trial (DCT) study designs. Pragmatic trials are designed to test the effectiveness of an intervention in a setting that resembles clinical practice. Prospective, randomized, POC research embeds studies into clinical care to compare treatments already approved and used in everyday practice.²¹ This design differs from observational, non-interventional studies that gather additional information on real-world effectiveness and safety rather than answer a research question.²² In pragmatic studies, separate study visits are usually not required, and most data is typically collected from the electronic health record (EHR) and claims data. This simplified approach addresses the most important questions for frontline clinicians and their patients.²³ DCTs are conducted across settings or sites rather than at a centralized research site. These studies increasingly leverage the use of technology for data collection, such as telehealth platforms, wearable devices, and other mobile technologies.²⁴ Modern-day studies should engage patient-participants with a person-centered trial design and engage people where they have the most trust and convenience.²⁵

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial illustrates how evidence generation can be integrated into health care using a focused, pragmatic POC trial design.²⁶ The study was streamlined to generate evidence in busy hospital settings with a large number of subjects, collecting only essential data derived from EHRs and focused on adverse event reporting.²⁷ Key design features of the RECOVERY trial,

²¹ Patsopoulos NA. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011;13(2):217-24. <https://doi.org/10.31887/DCNS.2011.13.2/npatsopoulos>.

²² Suvarna V. Phase IV of Drug Development. *Perspect Clin Res*. 2010 Apr;1(2):57-60.

²³ Coalition for Advancing Clinical Trials at the Point of Care. *Advancing Clinical Trials at the Point-of-Care: Building a Platform to Give Patients and Clinicians Needed Evidence for Better Care*. actpoc.org. Published November 9, 2021. Accessed August 23, 2023. <https://actpoc.org/updates/letter-from-the-coalition/11-9-2021>

²⁴ Van Norman GA. Decentralized Clinical Trials: The Future of Medical Product Development *JACC Basic Transl Sci*. 2021 Apr 27;6(4):384-387. <https://doi.org/jacbsts.2021.01.011>.

²⁵ Hernandez A. Bending the Curve: Having the Trial Meet the Patient! *Good Clinical Practice: Considerations for Trials with Pragmatic or Decentralized Features*. September 13, 2023. <https://reaganudall.org/news-and-events/events/good-clinical-practice-considerations-trials-pragmatic-or-decentralized>

²⁶ Pessoa-Amorim G, Campbell M, Fletcher L, et al. Making Trials Part of Good Clinical care: Lessons from the RECOVERY Trial. *Future Healthcare Journal*. 2021;8(2):e243-e250. doi:<https://doi.org/10.7861/fhj.2021-0083>

²⁷ RECOVERY. Follow-up Data Collection. www.recoverytrial.net. Published 2023. Accessed October 1, 2023. <https://www.recoverytrial.net/for-site-staff/follow-up-data-collection#:~:text=ADVERSE%20EVENT%20REPORTING>

applicable to future post-market prospective POC studies, are provided in Table 3. Using principles of quality-by-design – focusing on key attributes of clinical trials that produce reliable, clinically meaningful results – promotes a systematic, transparent approach to evidence generation.^{28,29}

Table 3: Key Design Features³⁰

Design Feature	Rationale
Randomized	<ul style="list-style-type: none"> ▶ Avoidance of systematic error (bias).
Large	<ul style="list-style-type: none"> ▶ Avoidance of play chance. ▶ Provide adequate statistical power to detect moderate, but important, treatment effects across a broad range of circumstances.
Simple	<ul style="list-style-type: none"> ▶ Focus on critical components of quality that preserve safety and reliability. ▶ Streamlined study procedures at set-up, training, recruitment, randomisation, treatment delivery and follow-up facilitate timely results for patients and protect busy healthcare staff. ▶ Do not include extraneous procedures.
Inclusive	<ul style="list-style-type: none"> ▶ Facilitates prompt recruitment. ▶ Provides translatable results for all patients (both in and outside the UK).
Objective clinical outcomes	<ul style="list-style-type: none"> ▶ Clinically relevant results. ▶ Resistant to bias. ▶ Allow data to linkage for complete follow-up.
Linkage to national healthcare datasets	<ul style="list-style-type: none"> ▶ Reduced data collection by local research teams. ▶ Complete follow-up improving study reliability. ▶ Rapid collection of data to inform data monitoring committee analyses. ▶ Low-cost long-term follow-up.
Collaborative	<ul style="list-style-type: none"> ▶ Buy-in from stakeholders at every level into study quality. ▶ Transparency facilitates trust in study procedures, safety and results. ▶ Resources are not wasted.
Robust web-based systems	<ul style="list-style-type: none"> ▶ Accessible to site staff. ▶ Reliable randomisation. ▶ Built-in options on online forms encourage consistency and completeness of data.
Data quality monitoring	<ul style="list-style-type: none"> ▶ Study procedures are subject to ongoing and continuous quality evaluation during the trial.
Trial oversight	<ul style="list-style-type: none"> ▶ Investigators at local hospital best placed to oversee high-quality study conduct locally. ▶ Experienced data monitoring committee meeting regularly provide reassurances on efficacy, accountability and safety.

Much of the discussion on evidence generation has been in three key areas: 1) integration of and access to high-quality data from clinical trials, EHRs, and other sources; 2) restructuring of the health care system to incentivize the involvement of frontline clinicians and a wider diversity of patients; and 3) addressing concerns regarding informed consent, privacy, and sharing of data. Each of these areas is addressed in this document. The FDA has varying degrees of influence or control over each via regulatory structures, e.g., regulations and guidance and the application of these structures by its review divisions.

²⁸ Pessoa-Amorim G, Campbell M, Fletcher L, et al. Making Trials Part of Good Clinical care: Lessons from the RECOVERY Trial. Future Healthcare Journal. 2021;8(2):e243-e250. <https://doi.org/10.7861/fhj.2021-0083>

²⁹ Califf RM, Cavazzoni P, Woodcock J. Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study. JAMA Intern Med. 2022;182(12):1243-1244. doi:10.1001/jamainternmed.2022.4810

³⁰ Pessoa-Amorim G, Campbell M, Fletcher L, et al. Making Trials Part of Good Clinical care: Lessons from the RECOVERY Trial. Future Healthcare Journal. 2021;8(2):e243-e250. <https://doi.org/10.7861/fhj.2021-0083>

As shown in Figure 1, the fragmented health care delivery system in the U.S. impedes our ability to generate new knowledge during care delivery and to learn from the experience of every patient. This report envisions a future where incentives and systems are aligned to enable continuous learning during care delivery for the benefit of current and future patients, as depicted in Figure 2.

Figure 1: Fragmentation of the Health Care Delivery and Clinical Research Systems³¹

The reality is we have is a disaggregated, fragmented system with lack of organization around common, transparent high-quality information

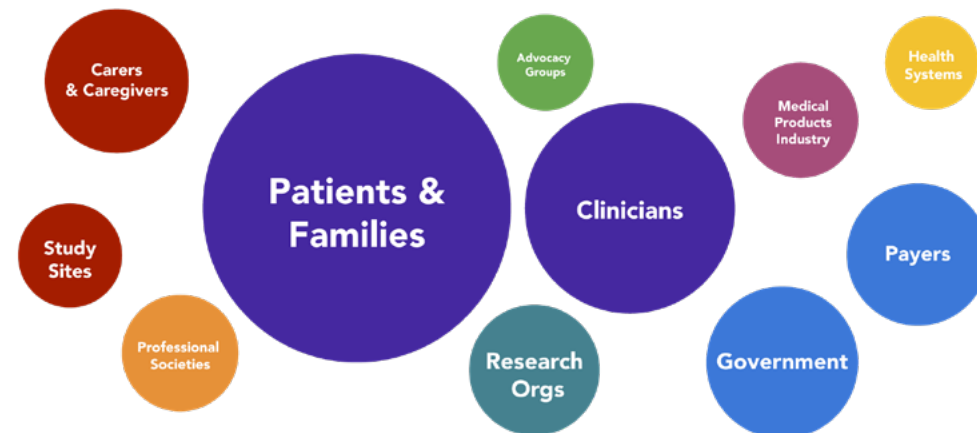
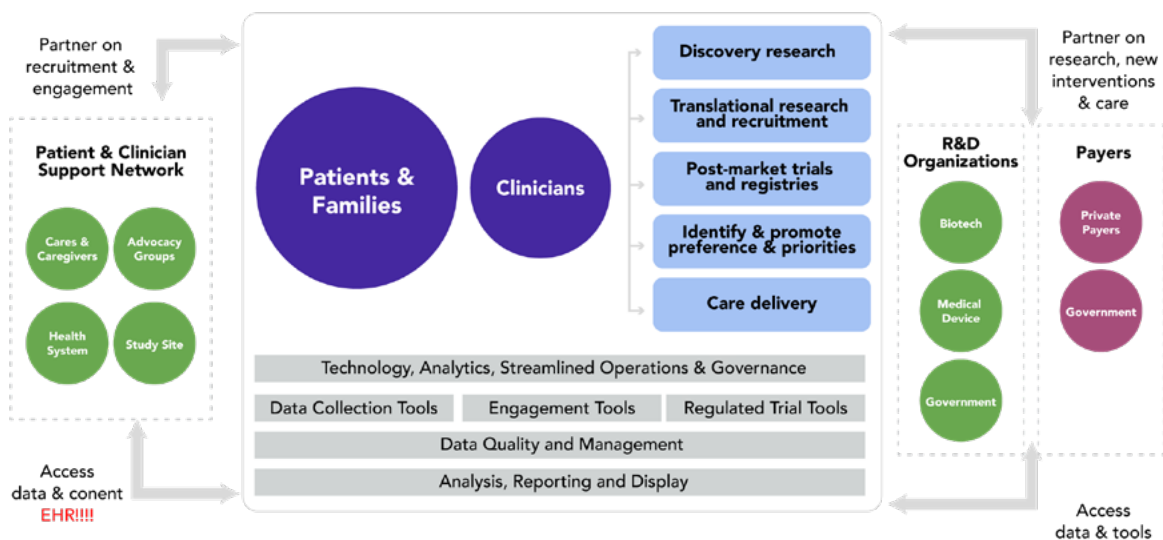


Figure 2: Possible Configuration of Components and Activities to Overcome System Fragmentation and Create a Highly Functional Health Care Delivery System and Clinical Research Enterprise³²

Given common goals, current technology could support a common information base that could support the primary mission: better outcomes for patients



³¹ Califf RM. Now is the time to fix the evidence generation system. *Clinical Trials*. 2023;20(1):174077452211476. doi:<https://doi.org/10.1177/17407745221147689>

³² Ibid

III. METHODOLOGY AND STAKEHOLDER INPUT

Expert Panel

Expert panel members were chosen based on their expertise related to evidence generation from a variety of perspectives. These perspectives included areas such as health systems, clinical research, implementation of pragmatic studies, informed consent, and clinical practice. The expert panel was charged with identifying changes for the FDA to consider in order to encourage and facilitate pragmatic evidence generation in the course of care delivery.

Roundtables

To inform the work of the expert panel, a series of roundtables (Appendix B) were conducted to explore topics related to evidence generation. The roundtables were small, invitation-only meetings and included experts (Appendix C) in a variety of fields. These individuals provided insights into what changes and incentives may be required for health systems, clinical researchers, clinicians, patient-participants, payers, sponsors, and information technology to support pragmatic evidence generation studies.

Utilizing use cases that illustrate the types of clinical questions that can be addressed by post-market pragmatic evidence generation studies (Appendix E) to stimulate discussion, the roundtable participants and expert panelists discussed current barriers to evidence generation. Participants also discussed potential solutions to overcome these barriers in order to inform regulatory decisions of the FDA and identify changes that the FDA may consider making to encourage evidence generation in the course of care delivery.

Roundtable Themes

1. Introductory Roundtable to Discuss the Generic Use Cases

The purpose of this discussion was to scope out the issues and obstacles of an evidence generation ecosystem using two hypothetical use cases. The outpatient use case involved repurposing a well-tolerated, FDA-approved drug to prevent diabetes; the inpatient scenario compared two pneumonia treatments. During this discussion, the panel members and guests discussed the elements that need to be addressed, such as financial incentives for health systems and clinicians, streamlining trial recruitment and informed consent, adapting EHR systems to capture clinical trial data, increasing patient diversity, involving community hospitals and outpatient clinics, and others, all within the context of POC clinical trials.

2. Financial Incentives for Health Systems, Payers, and Sponsors

The purpose of this discussion was to identify financial incentives for health systems, payers, sponsors, and clinicians. To encourage evidence generation, we need to look more closely at the barriers that impede post-market evidence generation and identify incentives to encourage it.

3. Engagement of Frontline Clinicians and Patients

The purpose of this roundtable was to discuss the recruitment of frontline clinicians in evidence generation projects. To ensure a robust diversity of patients who are representative of the intended use of these products, clinicians (those with prescribing authority, i.e., medical doctors (MDs), nurse practitioners (NPs), physician assistants (PAs), and pharmacists) should come not just from academic medical centers but also community hospitals, outpatient clinics, and pharmacies.

4. Streamlining Trial Recruitment and Informed Consent

The purpose of this roundtable was to discuss the recruitment of patients into evidence generation studies. To ensure a diverse population of patients who are representative of the individuals intended to use the products, we need to look for ways to lower the burden on patients who are enrolled in these studies, including streamlining informed consent and eliminating the need for extraneous medical appointments and testing.

5. EHR Systems and Other Forms of Data Collection

The purpose of this roundtable was to discuss how to leverage existing EHR systems to capture the relevant data elements in an evidence generation system and determine the obstacles to modifying EHR systems to add additional structured data elements if needed. Other topics included data interoperability and digital tools to facilitate the recruitment, onboarding, and randomization of patient-participants.

6. Other Regulatory and Legal Issues

The purpose of this roundtable was to hear the perspectives of sponsors on the opportunities and challenges in evidence generation studies, particularly post-market outcome trials conducted in a variety of health care settings. The focus of the discussion was on integration of and access to high-quality data and incentivizing the involvement of frontline clinicians and patient-participants from a variety of backgrounds, as well as generating recommendations for the FDA and other stakeholders on how to enable and/or facilitate conducting prospective, post-market trials in the course of routine clinical care.

Listening Sessions

Listening sessions were also held with clinicians and patient-participants to gauge their interest in research participation (Appendix D).

The primary objective of the Clinician Listening Sessions was to directly hear from frontline clinicians about obstacles and disincentives to their participation in POC clinical studies. Two 90-minute listening sessions were conducted among eight clinicians (five physicians, two nurse practitioners, one nurse) in the first session and 11 clinicians (seven physicians, four nurses) in the second session.

The primary objective of the Patient Listening Session was to determine key motivators and barriers to participating in clinical research, while also obtaining feedback on two different approaches to clinical research (outpatient and inpatient settings). A 90-minute listening session was conducted among eight patients who fit into one of the following three groups: 1) never considered participation in clinical research, 2) considered participation in clinical research, but did not participate, and 3) participated in clinical research.

IV. RECOMMENDATIONS

Overarching Recommendations

1. Many aspects of pragmatic evidence generation in the post-market setting need to be simplified to facilitate a more efficient and effective evidence generation strategy for the United States. These include, whenever possible, simplifying protocol objectives and endpoints to focus on clinically meaningful outcomes, broadening eligibility criteria, and streamlining adverse event reporting and required data collection. In addition, reducing the administrative requirements to encourage greater participation will require simplifying site and investigator/research staff credentialing, study-specific training, site initiation requirements, and the informed consent process. Creating and implementing standard, structured clinical data elements and automating electronic data capture is necessary to ensure success if pragmatic studies conducted in the post-market setting are to be successful and resource efficient.
2. An inter-agency taskforce should be established, led by FDA and comprised of FDA, NIH, CMS, ONC, and sponsors (e.g., industry, ARPA-H) to establish guiding principles and minimum requirements for post-market evidence generation studies that allow each agency to achieve its mandate while simplifying the entire evidence generation process.

Creation of clinical care-based knowledge generation requires a fundamental redesign and reengineering of how pragmatic evidence generation for regulatory purposes is done. Creating such a system will require coordinated effort across multiple agencies within HHS – not just the FDA, but also CMS, CDC, NIH, ONC – and new expectations for EHR vendors, providers, payers, and industry.

Creating an Environment for Pragmatic Evidence Generation

Observation

The phrase ‘clinical trial’ invokes a convention with ingrained terminology and procedures that imply complexity and large operational costs, particularly for trials that involve investigational products, i.e., products without regulatory approval. Sponsors and investigators need clear guidance on the regulatory pathway(s) by which post-market evidence generation studies can provide data acceptable for regulatory review.

Recommendations

3. Create a pragmatic evidence generation lexicon that distinguishes post-market evidence generation studies from pre-market (e.g., phase 1, 2 or 3) clinical trials, to use in guidance and other regulatory documents.
4. Utilize existing, and, if necessary, create new, regulatory programs that promote use and expedited review of post-market pragmatic evidence generation studies to support expanded indications, label changes, or to meet other regulatory requirements.

Discussion

Ambiguous terminology is a source of error and waste in our clinical research system.³³ Persistent use of ‘clinical research’ or ‘clinical trial’ language in the setting of pragmatic evidence generation may cause confusion among stakeholders as to how pre-market clinical trials differ from post-market evidence generation studies. The language used needs to help people step out of the pre-approval clinical trial world into a new environment. A collaboration between the FDA and the National Institutes of Health to standardize research terminology should include a lexicon clearly related to post-market pragmatic evidence generation, overlapping with phase 1 through 4 clinical trial language only where necessary.

FDA flexibility allows sponsors to engage with the FDA to determine if a study design or research methodology is acceptable for submission.³⁴ Roundtable participants, however, reported that such engagement does not always result in consistent advice and recommendations across centers or review divisions. Sponsors should be provided with clear, concrete, and consistent guidance as to the approval pathway to be used in order to conduct a post-market pragmatic evidence generation study that is acceptable for regulatory review.

³³ Califf RM, Cavazzoni P, Woodcock J. Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study. *JAMA Intern Med.* 2022;182(12):1243–1244. doi:10.1001/jamainternmed.2022.4810

³⁴ FDA Center for Drug Evaluation and Research, FDA Center for Biologics Evaluation and Research, FDA Oncology Center of Excellence. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry Real-World Data/Real-World Evidence (RWD/RWE).; 2023. <https://www.fda.gov/media/171667/download>

Implementation of Pragmatic Evidence Generation Studies

Observation

Not all post-market research questions can, or should, be answered using pragmatic study designs. One approach is to “adopt the features of pragmatic trials whenever feasible and sensible and when such features do not compromise trial quality and the ability to answer the clinical question of interest.”³⁵

In some situations, exposure to approved products may be very limited post market, and post-market pragmatic studies may not be appropriate. This might be the case, for example, if a product is approved for a specific oncology indication but is then studied post market for a new indication in a broader population with a different risk tolerance, such as studying an agent approved for treatment of a rare cancer as a cancer prevention agent in a high-risk population without cancer. However, in many situations, pragmatic evidence generation could be appropriate, for example when a drug indicated for the treatment of diabetes is studied for prevention of progression of pre-diabetes to overt diabetes or cardiovascular outcomes. In this case, a more efficient and effective streamlined approach integrated into care delivery and not a stand-alone, parallel activity, should be considered.

Recommendations

5. Clearly articulate and demonstrate a value proposition for health care leaders to support the incorporation of pragmatic evidence generation studies into routine clinical care. The value proposition should incorporate payment systems that support clinician participation in pragmatic evidence generation studies (e.g., research relative value units (RVUs)), as well as support for essential research infrastructure. Participation in pragmatic evidence generation should be considered a quality metric for payers, health systems, and individual providers. Other components of integration should include changes to the EHR system to standardize data in EHRs, enable data interoperability, enhance data quality, and automate reporting of quality measures.
6. Emphasize the importance of stakeholder engagement – explicitly define roles of, and obtain input from, frontline clinicians, patient-participants, and patient-participant family members or caregivers at the time of study design and implementation to facilitate collaboration and to seamlessly integrate the pragmatic evidence generation study into clinical care.

³⁵ Ford I, Norrie J. Pragmatic Trials. N Engl J Med 2016;375:454-463.

Discussion

Research infrastructure exists, but is often distinct and separate from clinical workflows and is conducted parallel to, rather than integrated within, the health care system. The push for pragmatic trials seeks to accomplish this integration and simplification of study operations. “A point-of-care trial is not a type of trial design, but rather an operational approach to integrate clinical research into routine health care delivery”³⁶ and “can also be applied to more seamlessly integrate with patients’ daily life, improve diversity in clinical trials, and more comprehensively ascertain patient-centered outcomes and clinical events.”³⁷

Pragmatic evidence generation embedded into routine clinical care, contextualized to the cultures within different clinical areas (e.g., emergency medicine vs. primary care vs. oncology), aims to generate new knowledge that improves clinical care and public health and benefits all stakeholders. Implementation will require a culture change that the FDA can catalyze and, in some cases, lead. Health system leaders and sponsors will need to develop value propositions relative to each stakeholder. For example, incentives to drive acceptance of pragmatic evidence generation studies may include payment systems that support research RVUs in addition to work RVUs. Implementation of quality metrics related to participation in clinical research makes it more enticing for health systems and providers to participate in these types of studies.

Data standardization and interoperability will be essential in leveraging EHR and claims data to support evidence generated from routine clinical care, thus eliminating the complexity of stand-alone study operations and parallel documentation systems. Such efforts require collaboration between the FDA, sponsors, ONC, and other government agencies. ONC’s Certification of Health IT³⁸ and the Trusted Exchange Framework and Common Agreement (TEFCA policy)³⁹ are good starting points on which to build this collaboration.

³⁶ Propes C, Locke T, Hendricks-Sturupp R. Improving Evidence Generation Through Point-Of-Care Trials. *Health Affairs Forefront* 2022. Accessed September 9, 2023. <https://doi.org/10.1377/FOREFRONT.20220819.260663>.

³⁷ 28. Duke Clinical Research Institute. DCRI Think Tanks Demonstrate What Is Possible. DCRI. Accessed September 25, 2023. <https://dcri.org/think-tanks/#:-:text=A%20point%2Dof%2Dcare%20trial>

³⁸ The Office of the National Coordinator for Health Information Technology (ONC). Certification of Health IT | HealthIT.gov. [www.healthit.gov. https://www.healthit.gov/topic/certification-ehrs/certification-health-it](https://www.healthit.gov/topic/certification-ehrs/certification-health-it)

³⁹ The Office of the National Coordinator for Health Information Technology (ONC). Interoperability | HealthIT.gov. [Healthit.gov. Published 2019. https://www.healthit.gov/topic/interoperability](https://www.healthit.gov/topic/interoperability)

Because of the variation in clinical practice, stakeholder input at the time of study design is essential to understand “usual care” and how study processes and data collection align with routine clinical workflows and visit documentation without creating additional work for the clinical care team. Patient-Focused Drug Development (PFDD) guidances⁴⁰ are complementary to, but should not be used in place of, patient input into a pragmatic study implementation strategy. Participants in the patient listening session also stressed the importance of including patients, or patient representatives, in the early stages of the design of clinical studies.

Health systems need to support approaches that improve clinician awareness of available studies and ensure that frontline clinicians and other members of the patient care team are supported and even incentivized to spend the time necessary to inform patients about the opportunity to participate in research studies. Clinicians are interested in being involved in evidence generation, but system-level and cultural barriers exist to such engagement. Often, there is not sufficient support for staff to conduct research and clinician workloads prohibit involvement in activities outside of clinical care. It is estimated that the mean time necessary for a primary care provider to provide guideline-recommended preventive, chronic disease and acute care to an average patient panel in solo practice or in a team-based care setting is 26.7 and 9.3 hours/day, respectively.⁴¹ Financial incentives alone will not overcome this time barrier. Incentives for participation in research studies by clinical care teams, voiced by clinician listening session participants, are listed in Table 4. Articulating how the study team interacts with clinicians and staff and role definitions for all involved needs to be established at the time of study design and prior to study implementation.

⁴⁰ Center for Drug Evaluation Research. CDER Patient-Focused Drug Development. FDA. Published July 27, 2021.

<https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development>

⁴¹ Porter J, Boyd C, Skandari MR, Laiteerapong N. Revisiting the Time Needed to Provide Adult Primary Care. *Journal of General Internal Medicine*. 2022;38(1). doi:<https://doi.org/10.1007/s11606-022-07707-x>

Table 4: Incentives for Clinical Care Team Participation in Pragmatic Evidence Generation Studies

- ▶ Inclusion of all staff while providing a sense of involvement and value in study operations
- ▶ Study operations cannot be too time-consuming or take away from patient care and support must be provided for any added tasks
 - "That it needs to be as absolutely easy as possible on my end. I don't have time. I barely have time for what I'm doing already."*
 - "...when we get into four or five patients an hour, you're not going to be able to pay me enough to be able to actually do my job and that."*
- ▶ A clear definition of the scope of the study and scope of clinical staff study roles prior to study implementation
- ▶ Clinical relevance to the clinician's patient population
 - "Then, ultimately, I mean the best litmus test that we have, of course, is 'is this going to really benefit our patients?'"*
- ▶ Timely communication about study results to clinicians and patient-participants

Observation

Sponsors and the FDA should minimize the time and cost burden to health care providers and the health care system for site initiation, training, and study-related procedures. Reducing the administrative burden of registering sites and investigators, when possible, will also facilitate implementation of pragmatic evidence generation studies.

Recommendations

7. Simplify site-related documentation and requirements related to study procedures (e.g., site questionnaires, temperature monitors).
8. The panel recommends a systematic approach to credentialing investigators and study personnel conducting post-market evidence generation studies and reducing the administrative burden associated with repeated registrations for each new study or with each new sponsor.
9. Consider creation of a centralized database of site credentials and credentialed investigators for post-market evidence generation studies to reduce the administrative burden of registering sites and investigators for every new study.
10. Develop master agreements between sponsors and sites to accelerate the contracting process and reduce time to trial launch.

Discussion

Simplifying post-market study designs and operating characteristics should improve alignment with the infrastructure needs for research and care delivery. Sponsors and

regulatory agencies should accept clinical credentials as sufficient in most cases to permit clinical staff to participate in post-market evidence generation studies and not require specialized research training. It is important to define study roles at the outset, distinguish who is permitted to obtain consent or collect data, and who takes responsibility for the trial. The necessary training should align with the individual's role in the study, its complexity and the risk to study participants.

Centralized databases of credentials reduce the requirement for investigators and sites to complete duplicative questionnaires, forms, trainings, and other requirements required by the FDA and other agencies for conducting clinical studies. Shared databases coupled with stakeholder collaboration will decrease the administrative and documentation burden of non-study specific tasks.⁴²

The FDA has issued draft guidance regarding implementation of DCTs for drugs, biological products and devices which address roles and responsibilities of the sponsor and study personnel.⁴³

Contracts are frequently negotiated individually for each site and each study, which unnecessarily increases time and effort for site startup. Streamlined approaches and unified "master" agreements are potential solutions.

Study Processes and Data Collection

Observations

The current research structure, including protocol design, data collection, and regulatory requirements, does not align with how clinical care is provided and may add only limited value to achieving the key study objectives. While pragmatic studies do try to align with clinical care, and the number of pragmatic studies is growing year-over-year, greater efforts should be made by sponsors and the FDA to align study requirements and procedures with routine clinical workflows and evaluations when appropriate.

Data collection for regulatory purposes in the context of post-market research can result in overcollection of information (beyond what is strictly needed to answer the study question), thus increasing documentation burden and the financial cost of evidence

⁴² The Site Qualification and Training (SQT) Initiative to reduce study-associated administrative burden. <https://www.transceleratebiopharmainc.com/initiatives/site-qualification-and-training/>

⁴³ Food and Drug Administration. Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability. 2023. 88 FR 27900. Accessed September 25, 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices>

generation studies. Requiring data collection and documentation beyond what is in the EHR and associated health care databases may diminish study acceptance and threaten protocol adherence.

The panel recognizes that EHR systems were not designed for clinical research and the lack of standard data elements both within and across platforms is a significant obstacle to data collection and analysis. ICD or CPT codes in claims data often do not match clinical descriptions in the EHR and adjudicating such discrepancies can be very time consuming. Evolving strategies for data standardization and interoperability between clinical, billing, and research systems, as discussed under Recommendation 5 above, will facilitate the use of EHR and claims data collected during pragmatic evidence generation studies.

Simplicity and focus are key for both acceptance and success of pragmatic evidence generation studies. Sponsors and the FDA should focus only on what information is necessary to answer the research question by designing studies with clearly stated and limited-in-number objectives and endpoints, utilizing standardized data that is readily available in the EHR and claims data, and does not always need to be manually adjudicated or validated during review.

Recommendations

- 11.** Whenever possible, required data elements should be available as structured data elements in the EHR or claims data. Align required data elements with clinical standards of care and design study protocols to collect data elements at time points consistent with clinical care guidelines and workflows.
- 12.** Inclusion and exclusion criteria and study endpoints should be written in a standardized (computable phenotype) format whenever possible to facilitate automatic matching of patient characteristics to clinical study requirements.
- 13.** EHR systems should be modifiable, where possible, to capture key health outcomes in a structured format. The clinical research community should work collaboratively with EHR vendors to create minimum common data elements for common diseases that capture important clinical descriptors and outcomes in a structured format.
- 14.** The FDA should consider issuing guidance on development, validation and use of algorithms to identify endpoints derived from EHR and/or claims data.
- 15.** The FDA, in collaboration with sponsors and other organizations, should maintain a library of commonly used and accepted algorithms for post-market pragmatic evidence generation.

16. Algorithms intended to be used in a post-market pragmatic evidence generation study should be pre-specified in the study protocol and discussed with the FDA prior to study launch.

Discussion

The panel recognizes that the context and regulatory objective determines whether a post-market pragmatic study design is feasible and fit-for purpose and ensures patient safety and data integrity. When appropriate, streamlined studies using pragmatic methods should be considered for post-market evidence generation. The FDA should consider accepting as documentation sufficient for regulatory review electronic databases that have been populated directly from structured data elements in the EHR and/or claims data, as outlined in the FDA's currently published guidance.⁴⁴

Key to pragmatic evidence generation is the development of straightforward, yet reliable, evidence to determine the impact of the intervention on a clinically meaningful endpoint or established surrogate. Data collection should include only variables necessary to answer the research question and assess the safety of the intervention being studied. In addition, standard of care assessments should be used in place of a complex research protocol to facilitate implementation, acknowledging that standards of care may vary among practice settings and should be considered at the time of study design. Current research that exemplifies the key design principles of pragmatic evidence generation include the RECOVERY trial (Table 3), Project Pragmatica,⁴⁵ and the Pragmatica-Lung Cancer Treatment Trial.⁴⁶

As previously noted, data standardization and interoperability will be essential in leveraging the EHR and claims data to support evidence generated from routine clinical care. Some of the difficulties plaguing the compatibility of EHRs for clinical and research use are being addressed by the mCODE initiative.⁴⁷ mCODE is a data standard that is being widely adopted to capture oncology data as structured data elements. It serves as a model for integrating clinical and research data elements and facilitates automatic matching of patient characteristics to clinical study requirements. Similar common data elements can be constructed for other therapeutic areas with the investigator community taking the lead to make this happen.

⁴⁴ FDA Center for Drug Evaluation and Research, FDA Center for Biologics Evaluation and Research, FDA Oncology Center of Excellence. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision- Making for Drug and Biological Products Guidance for Industry DRAFT GUIDANCE.; 2021. <https://www.fda.gov/media/152503/download>

⁴⁵ Office of the Commissioner, Oncology Center of Excellence. Project Pragmatica. Published March 23, 2023. Accessed September 25, 2023. <https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica>

⁴⁶ National Cancer Institute. Pragmatica-Lung Cancer Treatment Trial - NCI. www.cancer.gov. Published March 9, 2023. Accessed September 25, 2023. <https://www.cancer.gov>

⁴⁷ MITRE Health. mCODE . Accessed September 26, 2023. <https://health.mitre.org/mcode/>

Furthermore, FDA review is expedited by having datasets that are in standard CDISC format. Supporting technology to move pragmatic datasets into CDISC, or an alternative acceptable format, should be a priority to facilitate the use of this evidence in regulatory decision-making. Again, such efforts require collaboration between the FDA, ONC, CMS, sponsors, investigators, and other government agencies.

The panel recognizes the importance of validating EHR and claims-based endpoints used for evidence generation but once validated for a specific purpose these validated endpoints should be accepted for new studies in similar patient populations without additional validation efforts.⁴⁸ Data collection using EHR and claims data that does not require additional adjudication or validation is important for implementation of an integrated, straightforward, and resource-effective pragmatic evidence generation study.

Guidelines for identifying and using valid algorithms are integral to post-market pragmatic evidence generation used in regulatory decision-making.⁴⁹ Using the FDA's Sentinel System⁵⁰ as a model, a library of commonly used and accepted algorithms for post-market pragmatic evidence generation could serve as a resource for future studies and facilitate a learning health system. Insurer billing and coding instructions can change over time which may affect documentation in the EHR and coding trends in claims data, therefore, algorithms will need regular review to ensure that the code-lists used to populate them are updated. Focus should be on developing a systematic process for validating EHR and claims endpoints that can be widely leveraged for future studies and utilizing algorithmic adjudication, in place of manual, where appropriate.

Observation

Sponsors and the FDA should minimize the time and cost burden to health care providers and the health care system for study-related procedures, including reporting of adverse events (AE)s and concomitant medications. AE reporting is labor intensive and requirements for AE reporting for pre-approval (e.g., phase 1, 2, or 3) studies may not be necessary for post-market pragmatic evidence generation studies of medical products with known safety profiles.

⁴⁸ Simon GE, Bindman AB, Dreyer NA, et. al. When Can We Trust Real-World Data To Evaluate New Medical Treatments? *Clin Pharmacol Ther* 2022;111(1):24-29.

⁴⁹ Curtis LH, Sola-Morales O, Heidt J, et. al. Regulatory and HTA Considerations for Development of Real-World Data Derived External Controls. *Clin Pharmacol Ther* 2023;114(2):303-315.

⁵⁰ Brown JS, Mendelsohn AB, Nam YH, et. al. The US Food and Drug Administration Sentinel System: a national resource for a learning health system. *J Am Med Inform Assoc* 2022;00(0):1-10. <https://doi.org/10.1093/jamia/ocac153>

Recommendation

17. Perform analyses of adverse events at the end of the study, using the EHR and/or claims data for event analysis, rather than requiring real-time reporting of AEs to the FDA by the frontline clinician within a specific time window during the study. Unexpected, high grade, treatment-related AEs and serious AEs (SAE)s should continue to be reported expeditiously by the study investigators.

Discussion

For post-market studies of products with a known safety profile, the real-time AE collection should be limited to unexpected, high grade, treatment-related AEs and SAEs. If a trained research coordinator is present, frontline clinicians can have a limited role in AE reporting such as determination of the relationship of the event to study treatment.

FDA “Guidance for Industry Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations” (Tables 5, 6)⁵¹ and the ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials⁵² support selective collection of AE data, taking into account benefit-risk considerations specific to the study while ensuring ongoing patient safety. Although the FDA has provided this guidance on targeted safety data collection, it has not been widely adopted by sponsors. FDA guidance also states, “Because they have been previously observed with a drug, the AEs listed in the investigator’s brochure would, by definition, not be considered unexpected and thus would not be unanticipated problems,” with the caveat that changes in the specificity, severity, or frequency of an AE is considered unanticipated.⁵³

Of note, RECOVERY utilized targeted safety data collection. AEs were reported in real time only if they were both a) serious, and b) believed to be related (with reasonable possibility) to the study treatment, in the opinion of the local principal investigator.

These guidances support the panel’s recommendation for streamlined AE reporting. Unanticipated, high-grade AEs and SAEs that occur in pragmatic evidence generation studies should continue to be reported in real time.

⁵¹ Federal Register, “Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry; Availability,” (81 FR 8509, February 19, 2016). Guidance at <https://www.fda.gov/media/82664/download>

⁵² European Medicines Agency, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Guideline E19 on a Selective Approach to Safety Data Collection in Specific late-stage pre-approval or post-approval Clinical Trials - Scientific. European Medicines Agency. Published June 10, 2022. Accessed September 26, 2023. <https://www.ema.europa.eu/en/ich-guideline-e19-selective-approach-safety-data-collection-specific-late-stage-pre-approval-post>

⁵³ Federal Register, “Reporting of Adverse Events to Institutional Review Boards; Public Hearing,” (70 FR 6693, March 21, 2005). Guidance at <https://www.fda.gov/media/72267/download>

Table 5: Appropriate Selective or Specifically Targeted Safety Data Collection

When the following conditions are present:

1. The number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
 2. The occurrence of adverse events has been generally similar across multiple studies
 3. There is a reasonable basis to conclude that the occurrence of AEs in the population to be studied will be similar to previously observed rates
-

Table 6: Safety Data That May Be Appropriate for Abbreviated Collection or Non-Collection

1. Non-serious AEs not associated with drug discontinuation
 2. Routine lab monitoring
 3. Information on concomitant medications
 4. History and physical exams
-

Observation

The FDA is open to more pragmatic studies. Sponsors and investigators would benefit from clear and definitive guidance regarding acceptable documentation and evidence generated from pragmatic, POC, DCTs, and comparative effectiveness studies.

Recommendations

- 18.** The FDA should issue guidance regarding the scope, scale, and quality of evidence they would consider from post-market pragmatic evidence generation studies to expand indications, modify labeling, or close evidence gaps for use of a marketed medical product, that is distinctive from guidance for pre-approval clinical trials for new medical products.
- 19.** Pragmatic evidence generation principles and processes as well as acceptable standards for study design, analysis, and data quality, need to be promulgated by FDA leadership and implemented at all levels/across all divisions within the FDA. The panel recommends that the FDA consider establishing internal review policies and procedures for reviewing pragmatic evidence generation studies distinct from those policies and procedures applied to pre-approval clinical research as well as engaging experts in pragmatic trials within the FDA in the review of submissions of pragmatic post-market studies.

20. The FDA and external stakeholders should devise a series of 'use cases' using minimal data collection as examples to demonstrate what would be acceptable for the FDA and sponsors to use for regulatory purposes, understanding that nuances do exist with each application.
21. Consider running pilot demonstration projects to test this innovative approach to pragmatic evidence generation with other agencies such as NIH, PCORI, CMS, or industry, that will serve the public health interests and/or meet a regulatory purpose, potentially as public-private partnerships between the FDA, publicly-funded research networks, health systems, payers, and industry.

Discussion

The panel recognizes that the type and quantity of evidence needed for post-approval indications or label modifications depends on the labeling objective and therapeutic context and that the FDA's evidentiary standard for effectiveness does not change based on a product's marketing status.

A modified roadmap is likely needed to guide FDA application review when evidence is generated from DCTs, pragmatic and POC studies using outcomes (e.g., myocardial infarction, stroke, or death) garnered from EHR and/or claims data. FDA requirements and expectations for all aspects of the pragmatic evidence generation process – investigator training, study methodology, documentation and data collection, AE reporting, and endpoint validation – need to be explicit, transparent, and consistently applied. Sponsors are driven by a fear of failure during FDA review and, therefore, invest in collecting enormous amounts of data, much of which is not necessary or informative. The fear comes, in part, from presumed expectations of FDA reviewers and misunderstandings of FDA guidances and their application during the review process.

Although the FDA has written guidances on evidence that can be used to support new claims for marketed products, a significant discrepancy exists between these guidances and the understanding and practices of sponsors. This discrepancy may be due to a lack of awareness that these documents exist or a lack of understanding of the document itself by sponsors. Additionally, sponsors may hesitate in following guidance because they are not confident that the FDA will apply the principles of the guidance during the review process. As mentioned earlier, roundtable participants reported that such engagement does not always result in consistent advice. Frequent interaction is necessary between sponsors and the FDA to reach a clear understanding of when and how the various guidances apply.

Significant expertise currently exists at the FDA in the review of post-market pragmatic studies. This expertise can be leveraged by creating a cross-center consultative group specifically for guidance and review of post-market pragmatic evidence generation studies.

Use cases describe system functions from the perspective of the end user using a scenario of steps the user takes to interact with a system. The availability of use cases will guide both FDA staff and sponsors to determine minimal data collection that is acceptable for use to expand indications, modify labeling or close evidence gaps. Post-market assessment case studies in “Successes and Opportunities in Modeling & Simulation for FDA”⁵⁴ demonstrate how modeling and simulation fits into the regulatory environment. Sponsors and study teams would benefit from similar use cases demonstrating how post-market pragmatic evidence contributes to successful applications.

Patient-Participant Recruitment and Enrollment

Observation

Time, geographic location, and financial commitments may prohibit study participation by some patients and exclude patients based on socioeconomic status and other social determinants of health.

Recommendations

- 22.** Reduce barriers to patient participation (e.g., allow some parameters/measurements to be obtained from the person’s home by video, telephone, or computer; increase use of wearable tracking/monitoring devices) and be more transparent about patient-level time and cost commitments.
- 23.** Reduce the cost of participation to patients by eliminating copays for standard of care treatments or otherwise reimbursing for study-related costs whenever possible.
- 24.** Incorporate community health centers, outpatient clinics, and community-based pharmacies into pragmatic evidence generation studies to recruit a greater diversity of patient-participants who are more reflective of the intended use population of the product being studied.

⁵⁴ Food and Drug Administration, Modeling & Simulation Working Group of the Senior Science Council. Successes and Opportunities in Modeling & Simulation for FDA; 2022. <https://www.fda.gov/media/163156/download>

Discussion

Not all post-market pragmatic evidence generation studies need to be conducted in the clinical care environment – DCTs can engage patient-participants at home, in pharmacies, or in another convenient setting.

To improve the diversity of participants in post-market evidence generation studies, study procedures and investigators need to be straightforward, respectful, transparent about commitments and expectations, and meet people where they are – e.g., regarding the use of technology, their trust in health care providers and the medical system, and/or concerns about potential drug side effects or adverse health effects.

During the clinician listening session, one participant voiced concern about enrolling patients in a study that may provide an effective treatment, then needing to discontinue that treatment when the study ends because the patient's insurance does not cover the medication. Clinicians also voiced that there is a high level of mistrust among minorities and disenfranchised patients surrounding research. In addition, recruitment information and study materials are often not written for patients with low health literacy, frequently excluding this population from study participation. Design of trials with approaches to improve the recruitment of study participants with limited English proficiency and/or lower health literacy skills is necessary in order to apply study results from pragmatic evidence generation trials to patient populations that comprise many practitioner panels.

"I just want to say something else about idea of the primary amount of research being done by the academic centers versus being done in a place where like your FQHC or in a private practice. If we don't try harder to get to these places, we're not going to have the right diversity and the right patient population. We're limiting it to the patient populations that academic centers serve." – provider quote

Participants in the patient listening session reported the primary motivation for participating in clinical studies is improved personal health, with the added benefit that the findings could also help others with a similar condition. The prospect of improved health outweighed financial compensation as a potential motivator for participation, though participants did voice that they expect to be reimbursed for any study-related out-of-pocket costs. *"...if they're not offering any assistance in terms of getting there, that would be a huge barrier."* The potential for side effects may also be a barrier to participation

and must be carefully weighed against the perceived benefits. *“For me, the risk potential would have to be very, very clearly assessed.”* Participants also expressed that it is important that the information regarding the clinical research process is presented in an easy-to-understand way.

Currently, under the Affordable Care Act (ACA), insurers are required to pay for routine clinical care costs in clinical trials and sponsors are required to pay for research-related procedures. Even though routine care expenses are covered by this mandate, patient-participants may still be responsible for co-pays and co-insurance portions that may be financially burdensome. The FDA has published guidance on reimbursement for incidental expenses.⁵⁵ Waiving copays is legally complicated to accomplish due to federal beneficiary inducement prohibitions and state level regulations involving insurance fraud. Although legally complicated, this should not preclude the pursuit of appropriate steps to cover co-pay and co-insurance costs incurred by participants in pragmatic evidence generation studies.

Observation

Especially in the setting of an already-approved and marketed product, the usual consent process is unnecessarily cumbersome with long, detailed consent forms which may not adequately convey the key pieces of information that patient-participants need to make informed choices about study participation. The consent process warrants restructuring to determine the best strategy for informing patients about a pragmatic evidence generation study and answering any questions they may have.

Recommendations

- 25.** The FDA should provide clarification and guidance on the necessary elements of informed consent for post-market evidence generation studies. An ideal consent form includes a short description containing key elements written in plain language, limited to one or two pages, and available in the language of the prospective patient-participant. Additional layers or modules that give patients options to delve deeper into the information can be added.
- 26.** Explore alternative methods for consent in the post-market evidence generation setting.

⁵⁵ Office of the Commissioner, Office of Clinical Policy and Programs, Office of Clinical Policy, Office of Good Clinical Practice. Payment and Reimbursement to Research Subjects. www.fda.gov. Published April 18, 2019. Accessed October 3, 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects#:~:text=While%20the%20entire%20payment%20should>

27. Explore separating provision of institutional liability language from the consent process to simplify and shorten consent documents.
28. Include the consent form in ClinicalTrials.gov registration to further learn about what works to streamline the informed consent process.

Discussion

Consent forms need to be short, written in plain language without medical jargon, and clearly state the potential risks and benefits from participating in the study. Consider the use of notifications of study participation using opt-out or opt-in options, depending on the exact type of study being conducted.

Some of the bulk in consent forms is institutional boilerplate. Separation of institutional-level consent language from the federal regulatory language may be of benefit. However, it is also important to avoid having double-barreled consent where patient-participants receive a short consent document following federal guidelines and then a long institutional form. FDA and Common Rule guidance address alternative consent methods, including waiver and alteration, potentially applicable to pragmatic evidence generation studies.^{56,57} Education of investigators about this guidance may be useful. Public availability of study consent forms, via ClinicalTrials.gov, “can facilitate development of best practices, make the process of drafting consent forms more efficient, and provide insight into how well consent forms are satisfying their mission of protecting and promoting the autonomy of trial participants.”⁵⁸

Health care providers (primary care or specialist) are trusted sources for advice when a person is considering whether to participate in a clinical study. Keeping the patient-participant’s primary care physician in the loop is important. Additionally, literature findings support a team-based approach to informed consent, in which physician-investigators and research coordinators promote both the understanding and voluntariness of prospective participants.⁵⁹

⁵⁶ Common Rule <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/revision-of-the-common-rule/index.html>

⁵⁷ Food and Drug Administration. Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability. 2023. 88 FR 27900. Accessed September 25, 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices>

⁵⁸ Lynch HF, Largent EA, Zarín DA. Reaping the Bounty of Publicly Available Clinical Trial Consent Forms. *IRB* 2017;39(6):10-15.

⁵⁹ Morain SR, Barlevy D, Joffe S, Largent EA. Physician-Investigator, Research Coordinator, and Patient Perspectives on Dual-Role Consent in Oncology. A Qualitative Study. *JAMA Netw Open* 2023;6(7): e2325477. doi:10.1001/jamanetworkopen.2023.2547

Funding Pragmatic Evidence Generation

Observation

All stakeholders – the health care system, clinicians, patients, payers, and sponsors – benefit from the results of pragmatic evidence generation studies, such as more efficient and lower cost clinical care. However, the cost of doing this work (infrastructure and additive cost in delivering service) is unsupported unless a sponsor funds it.

Recommendations

29. Sponsors, payers, federal agencies, and health care systems each benefit from evidence generated by pragmatic, point-of-care studies and DCTs. Whether through financial or material contributions (e.g., accelerated administrative pathways, data sharing, or use of research RVUs), these stakeholders should be expected to contribute significantly to the pragmatic evidence generation process. Examples such as coverage with evidence development studies provide precedent for payers to help support the generation of new information in the post-market setting.
30. Funding pragmatic evidence generation studies may need to extend beyond the typical product sponsor approach. The federal government may need to fund initial pragmatic evidence generation studies for regulatory acceptance to establish a precedent.

Discussion

The FDA has set a precedent for collaboration and co-funding of projects, contributing to a learning health system, via use of the Sentinel System. Collaborations have included the use of pragmatic study designs,^{60,61} and comparative effectiveness research.^{62,63} PCORnet RELIANCE, linking trial data with the Medicare fee-for-service data to provide additional information on primary and select secondary outcomes, is co-funded by the FDA and PCORnet.⁶⁴ Pragmatica-Lung,⁶⁵ a collaborative effort between NCI, FNIH, two pharmaceutical companies, and the FDA OCE, is an example of a public-private partnership that addresses an important clinical question in lung cancer with a simple trial design and minimal data collection.

60 Panozzo CA, Curtis LH, Marshall J, et al. Incidence of statin use in older adults with and without cardiovascular disease and diabetes mellitus, January 2008–March 2018. *PLoS One* 2019; 14(12):e0223515.

61 Garcia CJ, Haynes K, Pokorney SD, et al. Practical challenges in the conduct of pragmatic trials embedded in health plans: lessons of IMPACT AFib, an FDA-catalyst trial. *Clin Trials* 2020; 17(4):360–7.

62 Wu AC, McMahon PM, Welch E, et al. Characteristics of new adult users of mepolizumab with asthma in the USA. *BMJ Open Res* 2021; 8 (1): e001003.

63 Lockhart CM, McDermott CL, Felix T, et al. Barriers and facilitators to conduct high-quality, large-scale safety and comparative effectiveness research: the Biologics and Biosimilars Collective Intelligence Consortium experience. *Pharmacoepidemiol Drug Saf* 2020; 29 (7): 811–3.

64 Sentinel Initiative. FDA-Catalyst Alignment with the CMS Linkage to the PCORI RELIANCE Trial. <https://www.lung.org/research/clinical-trials/find-a-clinical-trial/reliance>

65 National Cancer Institute. Pragmatica-Lung Cancer Treatment Trial - NCI. [www.cancer.gov](https://www.cancer.gov/types/lung/research/pragmatica-lung-cancer-trial). Published March 9, 2023. Accessed September 25, 2023. <https://www.cancer.gov/types/lung/research/pragmatica-lung-cancer-trial>

These precedents establish a foundation for post-market evidence generation methodologies, data collection, and outcome analysis. Establishing a mechanism to prioritize this work will be necessary, and funding responsibility falls on all stakeholders to find new ways to select and pay for critical public interest studies.

V. CONCLUSION

This report outlines recommendations for changes that can be made by the FDA and other stakeholders to facilitate and support post-market pragmatic evidence generation studies that answer clinically meaningful questions in a timely manner and provide data of sufficient quality to enable regulatory decisions. All stakeholders within the health care ecosystem have an obligation to generate new knowledge that improves clinical care or public health, and all will benefit by doing so.

In order to build a pragmatic evidence generation system, significant changes are needed in how post-market clinical research is conducted.

Attributes integral to pragmatic evidence generation include the following:

- ▶ Studies embedded into and aligned with clinical care and accessible to community sites that serve diverse patient populations
- ▶ Person-centered rather than institution-centered research objectives and endpoints
- ▶ Simple and focused study designs with limited-in-number clinically relevant objectives and outcome measures
- ▶ Streamlined data collection and reporting using electronic health record systems and databases
- ▶ Rapid dissemination of new findings to payers and clinicians to secure reimbursement and stimulate use in practice

Leveraging the health care delivery ecosystem to enable and support post-market evidence generation will require concerted effort and commitment by health system leaders, clinicians, sponsors, payers, research funders, and regulatory agencies. The FDA can serve as the catalyst for engagement and interaction among these parties to transform the currently fragmented approach to post-market evidence generation into a far more systematic activity. The pragmatic evidence generation framework envisioned, if implemented, has the potential to rapidly close gaps in clinical evidence, expand the safe and effective use of medical products to populations underrepresented in registration-directed clinical trials, identify new uses for marketed products, and engage patients as active participants in knowledge generation. The vision of the learning health care system is to learn from the experience of every patient and to apply that knowledge for the benefit of all patients. The evidence generation framework recommended in this report will help bring this vision to reality.



Appendices





APPENDIX A

Appendix A

Panelist Biographies

Richard L. Schilsky, MD, FACP, FSCT, FASCO, (Chair), is the former Chief Medical Officer of the American Society of Clinical Oncology and Professor emeritus at University of Chicago. At the University of Chicago, Dr. Schilsky rose to the rank of Professor of Medicine (tenured) and served as Director of the University of Chicago Cancer Research Center (1991-99), as Associate Dean for Clinical Research (1999-2007) and as Chief of the Section of Hematology-Oncology (2009-2012). From 1995-2010, Dr. Schilsky also served as Chairman of the Cancer and Leukemia Group B, an NCI-sponsored national cancer clinical trials group. He has served as chair of the NCI Board of Scientific Advisors and as a member of the Clinical and Translational Research Advisory Committee. Dr. Schilsky also served as a member and chair of the Oncologic Drugs Advisory Committee of the Food and Drug Administration. Dr. Schilsky has served as a member of the Board of Directors of the American Society of Clinical Oncology (ASCO) and of the Conquer Cancer Foundation of ASCO and as ASCO President 2008-2009. He currently serves as Chair of the Board of Directors of the Reagan-Udall Foundation for the FDA.

Judith Currier, MD, MSc, University of California-Los Angeles, is Professor of Medicine in the Division of Infectious Diseases, Department of Medicine. She is also the Executive Vice Chair for Research in the Department of Medicine, the Co-Director of the UCLA Center for Clinical AIDS Research and Education (CARE) and the Sue and Michael Steinberg Chair in Global AIDS Research. She served as Chief of the Division of Infectious Diseases at UCLA from 2010-2013 and has served as the PI and Chair of the AIDS Clinical Trials Group since 2017. Dr. Currier is trained both in Infectious Diseases and Clinical Epidemiology, and her research interests include the treatment and prevention of complications of antiretroviral therapy, gender-related issues in HIV therapy and the evaluation of antiretroviral treatment strategies globally.

Richard J. Gilfillan, MD, MBA, Trinity Health (retired), has been a practicing family physician, an integrated health system CEO, and an Insurance Company executive during his 30-year career. Dr. Gilfillan was the CEO of Trinity Health System from 2013 to 2019. Prior to that, he was a deputy administrator of the Centers for Medicare and Medicaid Services and director of the Center for Medicare and Medicaid Innovation from 2010 to 2013. He has served in a variety of senior roles across the industry including President and CEO of Geisinger Health Plan and Executive Vice President of insurance operations for Geisinger Health System, Senior Vice President for national contracting at Coventry Health Plan, General Manager of AmeriHealth New Jersey, and Chief Medical Officer of Independence Blue Cross. In 2018, he played a leading role in the creation of Civica Rx, a non-profit committed to increasing access to critical medications. He currently serves as an At Large Trustee on the United States Pharmacopeia (USP) Board of Trustees.

Robert A. Harrington, MD, is a cardiologist and the Stephen and Suzanne Weiss Dean of Weill Cornell Medicine and provost for medical affairs of Cornell University. He was previously the Arthur L. Bloomfield Professor and Chairman of the Department of Medicine at Stanford University and Richard Stack Distinguished Professor and the Director of the Duke Clinical Research Institute (DCRI) at Duke University. He has served as a member and the chair of the US Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee and is a member of the American Heart Association's (AHA's) Board of Directors. He served as AHA President-elect, President, and Immediate Past President during 2019-2021. His research involves building local, national, and international collaborations for the efficient conduct of innovative clinical research and trying to better understand and improve upon the methodology of clinical research, including the use of technologies to facilitate the conduct of clinical trials.

Adrian Hernandez, MD, MHS, is a cardiologist who serves as the Executive Director, Duke Clinical Research Institute, and Vice Dean for Clinical Research, Duke University School of Medicine. Dr. Hernandez was previously the Director of Health Services and Outcomes Research at the Duke Clinical Research Institute (DCRI). Dr. Hernandez has devoted his career to research in order to improve population health, focusing on understanding health outcomes, and closing the gap between clinical efficacy and effectiveness. An expert in trial design, use of electronic health data, health services, and regulatory science, Dr. Hernandez has led efforts to create more pragmatic clinical trials that get closer to what patients and clinicians experience every day. Presently, he is the Coordinating Center Principal Investigator for PCORI's National Patient-Centered Clinical Research Network (PCORnet), NIH's Health System Collaboratory, and other pragmatic clinical trials to generate real-world evidence. He is also the Coordinating Center Principal Investigator for the Baseline Health System Consortium which aims to change how clinical research is performed to integrate people in and outside of the health system, accelerate research, and improve efficiency.

Emily A. Largent, JD, PhD, RN, University of Pennsylvania, is the Emanuel and Robert Hart Assistant Professor of Medical Ethics and Health Policy in the Perelman School of Medicine. She holds a secondary appointment at Penn Law, is a senior fellow at the Leonard Davis Institute of Health Economics and is part of the Center for Health Incentives and Behavioral Economics (CHIBE). Prof. Largent's work explores ethical and regulatory aspects of human subjects research with a particular focus on Alzheimer's disease research and the translation of research findings into care. She presently co-leads the Ethics and Regulation Core of the NIA-funded IMPACT Collaboratory, which seeks to build capacity to conduct pragmatic trials aimed at generating real-world evidence to improve the lives of people living with dementia and their care partners. She is a member of the Patient-Centered Outcomes Research Institute (PCORI) Clinical Trials Advisory Panel.

Russell Rothman, MD, MPP, is a primary care physician and an expert in health services research and health communication. Dr. Rothman is Professor of Internal Medicine, Pediatrics and Health Policy, Ingram Professor of Integrative and Population Health, and the Senior Vice President for Population and Public Health at Vanderbilt University Medical Center. He also serves as the Director of the Institute for Medicine and Public Health and Associate Dean for Population Health Sciences. Dr. Rothman served as Chair of the PCORI PCORnet Executive Steering Committee and is currently the Principal Investigator of the STAR (Stakeholders, Technology and Research) Clinical Research Network. Dr. Rothman served as Co-Chair of the Steering Committees of the ADAPTABLE study, a pragmatic clinical trial, and the Healthcare workers Exposure Response and Outcomes (HERO) Study. He is also the past president of the Academy of Communication in Healthcare (ACH).

Joanne Waldstreicher, MD, was the Chief Medical Officer at Johnson & Johnson with oversight across pharmaceuticals, devices and consumer products for safety, epidemiology, clinical and regulatory operations transformation, collaborations on ethical science, and technology and R&D policies, including those related to clinical trial transparency and compassionate access. She chaired the R&D Development Pipeline Review Committee for The Janssen Pharmaceutical Companies of Johnson & Johnson and supported the Medical Devices and Consumer Development Committees. Before joining Johnson & Johnson in 2002, she headed endocrinology and metabolism clinical research at Merck Research Laboratories. Dr. Waldstreicher is currently an independent board member of Becton Dickinson and Structure Therapeutics, a consultant for pharmaceutical companies, and a faculty affiliate of the Division of Medical Ethics, Department of Population Health, New York University School of Medicine.



APPENDIX B

Appendix B

Evidence Generation Roundtables

- | | |
|----------------------|---|
| Roundtable #1 | EXPLORING OBSTACLES TO EVIDENCE GENERATION
March 13, 2023
3-4:30 pm ET |
| Roundtable #2 | FINANCIAL INCENTIVES FOR HEALTH SYSTEMS,
PAYERS, SPONSORS, AND CLINICIANS
April 11, 2023
9-10:30 am ET |
| Roundtable #3 | ENGAGEMENT OF FRONTLINE CLINICIANS
May 8, 2023
3-4:30 pm ET |
| Roundtable #4 | PATIENT RECRUITMENT AND INFORMED CONSENT
June 6, 2023
11 am–12:30 pm ET |
| Roundtable #5 | ELECTRONIC HEALTH RECORDS AND DATA COLLECTION
July 10, 2023
3-4:30 pm ET |
| Roundtable #6 | SPONSOR PERSPECTIVES
August 7, 2023
3-4:30 pm ET |



APPENDIX C

Appendix C

Roundtable Participants

Alpert, Susan

Anderson, Brian

Bierer, Barbara

Booth, Lisa Simms

Brennan, Troyen

Brown, Samuel

Byrne, Jennifer

Byrne, Katherine

Carroll, Jim

Carson, Jeff

Clemens, Daniel

DiCicco, Rob

Gagne, Joshua

Gelinas, Luke

Gomez-Caminero, Andres

Greenberg, Leslie

Griggs, Jackson

Huff, Stanley

Johnston, Joseph

Klein, Natalie

Landray, Martin

Lin, Sue

Lindemann, Phil

List, James

Lundstrom, Tammy

Lynch, Holly Fernandez

Mangione, Carol

Masoudi, Frederick

McClellan, Mark

Melhem, Fareed

Meropol, Neal

Mirhaji, Parsa

Moscicki, Richard

Musen, Mark

Roe, Laura

Sherman, Michael

Smider, Nancy

Tandon, Ramita

Valin, JP

Wei, Henry



APPENDIX D

Appendix D

Listening Sessions

LISTENING SESSION #1 HEALTH CARE PROFESSIONALS

May 4, 2023

7 pm ET

LISTENING SESSION #2 PATIENTS

June 28, 2023

7 pm ET

LISTENING SESSION #3 HEALTH CARE PROFESSIONALS

September 26, 2023

7 pm ET



APPENDIX E

Use Case 1

Description: Outpatient trial of a marketed drug (Drug X) used to treat type 2 diabetes to determine effectiveness, tolerability and adherence when used to delay progression from pre-diabetes to type 2 diabetes in adults

Hypothesis: Drug X will be more effective than standard diet/exercise counseling in delaying progression from pre-diabetes to type 2 diabetes in adults

Inclusion Criteria: Adult patients diagnosed with pre-diabetes per American Diabetes Association criteria (A1C, fasting blood sugar tests)

Trial Design: Eligible patients randomized 1:1:1 drug intervention plus standard diet/exercise vs. metformin plus standard diet/exercise vs. standard diet/exercise counseling alone

Primary Endpoint: Percentage of patients diagnosed with type 2 diabetes, as measured by A1C, FPG, at 24, 48 and 60 months

Secondary endpoints: Focus on content of EHRs/other clinical records. Patient adherence to treatment program, serious adverse events (SAE), diagnosis of acute MI, stroke, renal failure, or diabetic retinopathy

Required Data Elements: A1C, FPG tests, SAEs, hospital admission, death (need to find death outside EHRs, e.g., death records), diagnosis of acute MI, stroke, renal failure or diabetic retinopathy

Length of Trial: 5+ years, depending on enrollment

Use Case 2

Description: Inpatient trial to assess comparative effectiveness of two approved treatments for community-acquired pneumonia

Hypothesis: One of two therapies (combination vs. monotherapy or two combination therapies) will perform significantly better in treating community-acquired pneumonia

Inclusion Criteria: Adult patients diagnosed with community-acquired pneumonia, requiring IV antibiotics and hospitalization. No risk factors for pseudomonas or MRSA

Trial Design: Cluster RCT or individual patient randomization

Primary endpoint: Survival

Secondary endpoints: Length of stay, ICU admission, SAEs (All taken from claims or EHRs)

Required Data Elements: Date of diagnosis, date of admission, date treatment began, names and dosage of medication(s), date of discharge, survival, SAEs

Length of Trial: Until patient recruitment target is met



APPENDIX F

Appendix F

Stakeholder Responsibilities for Implementation

Stakeholders include the FDA, other Government Agencies (NIH, CDC, ONC), Payers (Private Insurance, Medicare, Medicaid), Industry/Sponsors & Other Funders (e.g., PCORI), Health Systems, EHR Vendors, Investigators, Professional Societies, Clinicians, Patients/Families

Recommendation	Stakeholders Responsible for Implementation
<p>1. Many aspects of pragmatic evidence generation in the post-market setting need to be simplified to facilitate a more efficient and effective evidence generation strategy for the United States. These include, whenever possible, simplifying protocol objectives and endpoints to focus on clinically meaningful outcomes, broadening eligibility criteria, and streamlining adverse event reporting and required data collection. In addition, reducing the administrative requirements to encourage greater participation will require simplifying site and investigator/research staff credentialing, study-specific training, site initiation requirements, and the informed consent process. Creating and implementing standard, structured clinical data elements and automating electronic data capture is necessary to ensure success if pragmatic studies conducted in the post-market setting are to be successful and resource efficient.</p>	FDA, Government Agencies, Payers, Industry/Sponsors, Funders, Health Systems, EHR Vendors, Clinicians
<p>2. An inter-agency taskforce should be established, led by the FDA and comprised of FDA, NIH, CMS, ONC, and sponsors (e.g., industry, ARPA-H) to establish guiding principles and minimum requirements for post-market evidence generation studies that allow each agency to achieve its mandate while simplifying the entire evidence generation process.</p>	FDA, Government Agencies, Industry/Sponsors, Funders
<p>3. Create a pragmatic evidence generation lexicon that distinguishes post-market evidence generation studies from pre-market (e.g., phase 1, 2 or 3) clinical trials, to use in guidance and other regulatory documents.</p>	FDA, NIH
<p>4. Utilize existing, and, if necessary, create new, regulatory programs that promote use and expedited review of post-market pragmatic evidence generation studies to support expanded indications, label changes or to meet other regulatory requirements.</p>	FDA

Recommendation

Stakeholders Responsible for Implementation

<p>5. Clearly articulate and demonstrate a value proposition for health care leaders to support the incorporation of pragmatic evidence generation studies into routine clinical care. The value proposition should incorporate payment systems that support clinician participation in pragmatic evidence generation studies (e.g., research relative value units (RVUs)), as well as support for essential research infrastructure. Participation in pragmatic evidence generation should be considered a quality metric for payers, health systems, and individual providers. Other components of integration should include changes to the EHR system to standardize data in EHRs, enable data interoperability, enhance data quality, and automate reporting of quality measures.</p>	<p>Health Systems, CMS, Payers, Clinicians, EHR vendors, FDA, Not-for-Profit Entities such as NCQA, and Professional Societies</p>
<p>6. Emphasize the importance of stakeholder engagement – explicitly define roles of, and obtain input from, frontline clinicians, patient-participants, and patient-participant family members or caregivers at the time of study design and implementation to facilitate collaboration and to seamlessly integrate the pragmatic evidence generation study into clinical care.</p>	<p>Industry/Sponsors, Funders, Government Agencies, Investigators, Patients, FDA</p>
<p>7. Simplify site-related documentation and requirements related to study procedures (e.g., site questionnaires, temperature monitors).</p>	<p>Industry/Sponsors, FDA</p>
<p>8. The panel recommends a systematic approach to credentialing investigators and study personnel conducting post-market pragmatic evidence generation studies and reducing the administrative burden associated with repeated registrations for each new study or with each new sponsor.</p>	<p>Industry/Sponsors, Funders, FDA, Health Systems</p>
<p>9. Consider creation of a centralized database of site credentials and credentialed investigators for post-market pragmatic evidence generation studies to reduce the administrative burden of registering sites and investigators for every new study.</p>	<p>FDA, Government Agencies, Industry/Sponsors</p>
<p>10. Develop master agreements between sponsors and sites to accelerate the contracting process and reduce time to trial launch.</p>	<p>Sponsors, Health Systems</p>
<p>11. Whenever possible, required data elements should be available as structured data elements in the EHR or claims data. Align required data elements with clinical standards of care and design study protocols to collect data elements at time points consistent with clinical care guidelines and workflows.</p>	<p>Industry/sponsors, Government Agencies, CMS, Health Systems, EHR Vendors</p>

Recommendation	Stakeholders Responsible for Implementation
<p>12. Inclusion and exclusion criteria and study endpoints should be written in a standardized (computable phenotype) format whenever possible to facilitate automatic matching of patient characteristics to clinical study requirements.</p>	<p>Industry/sponsors, Government Agencies, CMS, Health Systems, EHR Vendors</p>
<p>13. EHR systems should be modifiable, where possible, to capture key health outcomes in a structured format. The clinical research community should work collaboratively with EHR vendors to create minimum common data elements for common diseases that capture important clinical descriptors and outcomes in a structured format.</p>	<p>Government Agencies, CMS, Health Systems, EHR Vendors, Investigators</p>
<p>14. The FDA should consider issuing guidance on development, validation, and use of algorithms to identify endpoints derived from EHR and/or claims data.</p>	<p>FDA, Government Agencies, CMS</p>
<p>15. The FDA, in collaboration with sponsors and other organizations, should maintain a library of commonly used and accepted algorithms for post-market pragmatic evidence generation.</p>	<p>FDA, Government Agencies</p>
<p>16. Algorithms intended to be used in a post-market pragmatic evidence generation study should be pre-specified in the study protocol and discussed with the FDA prior to study launch.</p>	<p>FDA, Industry/Sponsors, Funders</p>
<p>17. Perform analyses of adverse events at the end of the study, using the EHR and/or claims data for event analysis, rather than requiring real-time reporting of AEs to FDA by the frontline clinician within a specific time window during the study. Unexpected, high grade, treatment-related AEs and serious AEs (SAE)s should continue to be reported expeditiously by the study investigators.</p>	<p>FDA, Clinicians, EHR Vendors</p>
<p>18. The FDA should issue guidance regarding the scope, scale and quality of evidence they would consider from post-market pragmatic evidence generation studies to expand indications, modify labelling or close evidence gaps for use of a marketed medical product, that is distinctive from guidance for pre-approval clinical trials for new medical products.</p>	<p>FDA</p>
<p>19. Pragmatic evidence generation principles and processes as well as acceptable standards for study design, analysis, and data quality, need to be promulgated by FDA leadership and implemented at all levels/ across all divisions within the FDA. The panel recommends that the FDA consider establishing internal review policies and procedures for reviewing pragmatic evidence generation studies distinct from those policies and procedures applied to pre-approval clinical research as well as engaging experts in pragmatic trials within FDA in the review of submissions of pragmatic post-market studies.</p>	<p>FDA</p>

Recommendation	Stakeholders Responsible for Implementation
<p>20. The FDA and external stakeholders should devise a series of ‘use cases’ using minimal data collection as examples to demonstrate what would be acceptable for the FDA and sponsors to use for regulatory purposes, understanding that nuances do exist with each application.</p>	<p>FDA, Industry/Sponsors, Funders, Investigators</p>
<p>21. Consider running pilot demonstration projects to test this innovative approach to pragmatic evidence generation with other agencies such as NIH, PCORI, CMS, or industry, that will serve the public health interests and/or meet a regulatory purpose, potentially as public-private partnerships between the FDA, publicly-funded research networks, health systems, payers, and industry.</p>	<p>FDA, Government Agencies, Industry/Sponsors, Funders, Health Systems</p>
<p>22. Reduce barriers to patient participation (e.g., allow some parameters/measurements to be obtained from the person’s home by video, telephone, or computer; increase use of wearable tracking/monitoring devices) and be more transparent about patient-level time and cost commitments.</p>	<p>Industry/Sponsors, Funders, Payers, Investigators, FDA, Patients/families</p>
<p>23. Reduce the cost of participation to patients by eliminating copays for standard of care treatments or otherwise reimbursing for study-related costs whenever possible.</p>	<p>Payers, Health Systems</p>
<p>24. Incorporate community health centers, outpatient clinics, and community-based pharmacies into pragmatic evidence generation studies to recruit a greater diversity of patient-participants who are more reflective of the intended use population of the product being studied.</p>	<p>Industry/Sponsors, Funders, Health Systems, Investigators</p>
<p>25. The FDA should provide clarification and guidance on the necessary elements of informed consent for post-market pragmatic evidence generation studies. An ideal consent form includes a short description containing key elements written in plain language, limited to one or two pages, and available in the language of the prospective patient-participant. Additional layers or modules that give patients options to delve deeper into the information can be added.</p>	<p>FDA, Government Agencies, Health Systems, Investigators, Patients</p>
<p>26. Explore alternative methods for consent in the post-market pragmatic evidence generation setting, e.g., notifications of study participation using opt-out or opt-in options, depending on the exact type of study being conducted.</p>	<p>FDA, Government Agencies, Health Systems, Investigators, Patients</p>
<p>27. Explore separating provision of institutional liability/patient protection language from the consent process to simplify and shorten consent documents.</p>	<p>Health Systems, Sponsors, FDA</p>

Recommendation**Stakeholders Responsible for Implementation**

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| 28. Include the consent form in ClinicalTrials.gov registration in order to further learn about what works to streamline the informed consent process. | Government Agencies, FDA |
| 29. Sponsors, payers, federal agencies, and health care systems each benefit from evidence generated by pragmatic, point-of-care studies and DCTs. Whether through financial or material contributions (e.g., accelerated administrative pathways, data sharing or use of research RVUs), these stakeholders should be expected to contribute significantly to the pragmatic evidence generation process. Examples such as coverage with evidence development studies provide precedent for payers to help support the generation of new information in the post-market setting. | FDA, Government Agencies, Payers, Industry/Sponsors, Funders, Health Systems |
| 30. Funding pragmatic evidence generation studies may need to extend beyond the typical product sponsor approach. The federal government may need to fund initial pragmatic evidence generation studies for regulatory acceptance to establish a precedent. | FDA, Government Agencies, CMS, Payers, Industry/Sponsors, Funders, Health Systems |
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