

MINI-SENTINEL and CLINICAL TRIALS TRANSFORMATION INITIATIVE
DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE
MINI-SENTINEL DISTRIBUTED DATABASE

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Workgroup Leads:

Richard Platt, MD, MSc,¹
Pamela Tenaerts, MD, MBA,²
Patrick Archdeacon, MD,³

Section Leads and Co-Authors:

Elizabeth Chrischilles, MS, PhD, (Leader and lead author of section: Capabilities and interest of the Mini-Sentinel Data Partners)⁴
Barbara Evans, PhD, JD, (Co-author of section: Data Privacy Considerations)⁵
Adrian Hernandez, MD, MHS, (Leader and lead author of section: Use Cases for Potential Studies)⁶
Deven McGraw, JD, LL.M., (Leader and co-author of section: Data Privacy Considerations)⁷
Cheryl McMahill-Walraven, MSW, PhD, (Co-lead and co-author of section: Capabilities and Interest of the Mini-Sentinel Data Partners)⁸
Marsha Raebel, PharmD, (Co-lead and co-author of section: Capabilities and Interest of the Mini-Sentinel Data Partners)⁹
Kristen Rosati, JD, (Co-author of section: Data Privacy Considerations)¹⁰

Workgroup Members: John Buse, MD, PhD,¹¹ Robert Califf, MD,¹² Niteesh Choudhry, MD, PHD,¹³ Scott Connor, BS,¹⁴ Jeffrey Curtis, MD, MS, MPH,¹⁵ Susan Ellenberg, PhD,¹⁶ Stephen Fortmann, MD,¹⁷ Kenneth Hornbuckle, DVM, MPH, PhD,¹⁸ Gabriella Lavezzari, PhD, MBA,¹⁹ Elliott Levy, MD,²⁰ Leanne Madre, JD, MHA,²¹ Elizabeth Mahon, JD,²² Edward Mannello, RPh, MBA,²³ J. Stephen Mikita, JD,²⁴ Alvin Mushlin, MD, ScM,²⁵ Vinit Nair, BSPHarm, MS, RPh,²⁶ Jane Perlmutter, PhD,²⁷ Bruce Psaty, MD, PhD,²⁸ Stephen Rosenfeld, MD, MBA,²⁹ Claire Spettell, PhD,³⁰

Workgroup Member Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA 2. Clinical Trials Transformation Initiative, Durham, NC 3. Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 4. University of Iowa, College of Public Health, Iowa City, IA 5. Center for Biotechnology & Law, University of Houston Law Center, Houston, TX 6. Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Durham, NC 7. Center for Democracy and Technology, Washington, DC 8. Aetna: Aetna Informatics, Blue Bell, PA 9. Kaiser Permanente Colorado, Denver, CO 10. Polsinelli, PC, Phoenix, AZ 11. Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, NC 12. Duke Translational Medicine Institute and Division of Cardiology, Duke University Medical Center, Durham, NC 13. Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 14. Acurian, Inc., Horsham, PA 15. Division of Clinical Immunology and

Rheumatology, University of Alabama at Birmingham, Birmingham, AL 16. Center for Clinical Epidemiology and Biostatistics, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 17. Center for Health Research Northwest, Kaiser Permanente Northwest, Portland, OR 18. Office of Risk Management and Pharmacoepidemiology, Global Patient Safety, Eli Lilly and Company, Indianapolis, IN 19. Scientific Affairs, Pharmaceutical Research and Manufacturers of America, Washington, DC 20. Global Pharmacovigilance and Epidemiology, Bristol-Meyers Squibb Co., Princeton, NJ 21. Clinical Trials Transformation Initiative, Durham, NC 22. Johnson and Johnson, New Brunswick, NJ 23. AstraZeneca, Wilmington, DE 24. Clinical Trials Transformation Initiative, Patient Representative, Steering Committee, Salt Lake City, UT 25. Weill Cornell Medical College, Department of Public Health, New York, NY 26. Humana: Competitive Health Analytics, Inc. Louisville, KY 27. Clinical Trials Transformation Initiative, Patient Advocate, Ann Arbor, MI 28. University of Washington, Seattle, WA 29. Quorum Review IRB, Seattle, WA 30. Aetna: Aetna Informatics, Blue Bell, PA

Supporting Staff: Aarthi Iyer, Project Manager, Harvard Pilgrim Health Care Institute, Boston, MA;¹ Jane Kolimaga, Project Manager, Clinical Trials Transformation Initiative, Durham, NC;² Nicholas Lehman-White, Research Assistant, Harvard Pilgrim Health Care Institute, Boston, MA;¹ MariJo Mencini, Staff Specialist, Clinical Trials Transformation Initiative, Durham, NC²

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Mini-Sentinel and Clinical Trials Transformation Initiative

Developing Approaches to Conducting Randomized Trials Using the Mini-Sentinel Distributed Database

Table of Contents

I. ABSTRACT	1
II. EXECUTIVE SUMMARY	2
A. INTRODUCTION	2
B. OPERATIONAL CHARACTERISTICS AND CONSIDERATIONS FOR RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE	2
C. BROAD THEMES NECESSARY FOR SUCCESS	3
1. <i>Stakeholder engagement</i>	3
2. <i>Defining clusters for cluster randomized designs</i>	3
3. <i>Centralized informed consent</i>	4
4. <i>Patient and provider participation and communication</i>	4
5. <i>Patient follow-up data</i>	4
D. USE CASES FOR POTENTIAL STUDIES WITH A DISTRIBUTED DATABASE	4
1. <i>Use Case #1: Strategy/Practice based: IMPACT-AF Clustered Randomized Trial (proposed by Christopher Granger, MD, and colleagues)</i>	4
2. <i>Use Case #2: Effectiveness of Discontinuing bisphosphonates (EDGE; proposed by Jeffrey Curtis, MD, MS, MPH)</i>	5
3. <i>Use Case #3: The Torsemide Risk Reduction versus Furosemide In Cardiac Insufficiency Trial (TERRIFIC; proposed by Eric Velazquez, MD, and colleagues)</i>	6
E. CAPABILITIES AND INTEREST OF THE MINI-SENTINEL DATA PARTNERS	6
1. <i>Previous experience</i>	6
2. <i>Willingness to participate in trials using the Mini-Sentinel infrastructure</i>	6
3. <i>Organizational and infrastructure needs</i>	7
4. <i>Identifying potential subjects</i>	7
5. <i>Identifying and engaging relevant clinicians</i>	7
6. <i>Contacting potential subjects</i>	7
7. <i>Using the Mini-Sentinel Distributed Database for exposures and outcomes</i>	7
8. <i>Obtaining full-text medical records</i>	8
9. <i>Summary of Data Partners' experience, capability, and willingness to participate in randomized clinical trials</i>	8
F. DATA PRIVACY CONSIDERATIONS	8
G. OVERALL CONCLUSIONS	9
III. INTRODUCTION	9
IV. EVALUATING THE POTENTIAL FOR CONDUCTING RANDOMIZED TRIALS IN PARTNERSHIP WITH MINI-SENTINEL DATA PARTNERS.....	11
V. CLINICAL TRIALS SUBGROUP REPORT: FRAMEWORK AND POTENTIAL USE CASES.....	11
A. CHARACTERISTICS OF PROTOCOLS FOR DISTRIBUTED RESEARCH NETWORK	11
B. OPERATIONAL CHARACTERISTICS AND CONSIDERATIONS FOR RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE	13

C.	NECESSARY CENTRALIZED EFFICIENCIES FOR RANDOMIZED CLINICAL TRIALS IN THE MINI-SENTINEL DISTRIBUTED DATABASE	14
1.	<i>Stakeholder engagement and approvals</i>	14
2.	<i>Defining clusters for cluster randomized designs</i>	15
3.	<i>Centralized informed consent</i>	15
4.	<i>Patient and provider participation and communication</i>	16
5.	<i>Patient follow-up data</i>	17
D.	USE CASES FOR POTENTIAL STUDIES WITH A DISTRIBUTED DATABASE	17
1.	<i>Use Case #1: Strategy/Practice based: IMPACT-AF Clustered Randomized Trial (proposed by Christopher Granger, MD, and colleagues)</i>	17
2.	<i>Use Case #2: Effectiveness of <u>Discontinuing</u> bisphosphonate<u>s</u> (EDGE; proposed by Jeffrey Curtis, MD, MS, MPH)</i>	20
3.	<i>Use Case #3: The Torsemide Risk Reduction versus Furosemide In Cardiac Insufficiency Trial (TERRIFIC; proposed by Eric Velazquez, MD, and colleagues)</i>	22
VI.	DATA SUBGROUP REPORT: MINI-SENTINEL RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE.....	25
A.	METHODS	25
B.	RESULTS: OVERALL IMPRESSION	25
1.	<i>Results: Previous experience</i>	25
2.	<i>Results: Willingness to participate in trials using the Mini-Sentinel infrastructure</i>	26
3.	<i>Results: Organizational and infrastructure needs</i>	27
4.	<i>Results: Identifying potential subjects</i>	27
5.	<i>Results: Identifying and engaging relevant clinicians</i>	28
6.	<i>Results: Contacting potential subjects</i>	28
7.	<i>Results: Using the Mini-Sentinel Distributed Database for exposures and outcomes</i>	28
8.	<i>Results: Obtaining full-text medical records</i>	29
C.	COMMENTS ABOUT THE THREE USE CASES	29
D.	CONCLUDING REMARKS.....	30
VII.	PRIVACY SUBGROUP REPORT: USES OF THE MINI-SENTINEL DISTRIBUTED DATABASE BEYOND SURVEILLANCE	30
A.	USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE TO “PREPARE FOR RESEARCH”	30
1.	<i>HIPAA requirements</i>	30
2.	<i>Common Rule requirements</i>	31
B.	USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE FOR PATIENT RECRUITMENT PURPOSES	31
1.	<i>HIPAA requirements</i>	31
2.	<i>Common Rule requirements</i>	32
C.	USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE TO CONDUCT RESEARCH	32
1.	<i>HIPAA and Common Rule research requirements – Internal uses of Protected Health Information</i>	32
a)	<i>Research uses with patient authorization</i>	32
b)	<i>Waivers of authorization requirement</i>	33
2.	<i>HIPAA and Common Rule requirements re: disclosures of research results</i>	34
a)	<i>De-identified data under HIPAA</i>	34
b)	<i>Common Rule and “de-identification”</i>	34
c)	<i>Disclosure of a Limited Data Set</i>	35
D.	NEW HIPAA RULES REQUIRING PRIOR PATIENT AUTHORIZATION FOR “SALE” OF PHI ARE NOT APPLICABLE	35

E.	ADDITIONAL USES OF THE MSDD AUTHORIZED BY FDAAA.....	36
1.	<i>Scope of authority for additional uses of Sentinel</i>	37
2.	<i>Statutory authority under FDAAA to use Sentinel to examine questions related to drug effectiveness</i>	38
3.	<i>The mechanics of allowing access to Mini-Sentinel for uses authorized in Section 355(k)(4)</i>	40
4.	<i>Privacy compliance for access pursuant to CDUAs</i>	40
F.	CONCLUSION OF DATA PRIVACY CONSIDERATIONS.....	41
VIII.	OVERALL SUMMARY WITH RECOMMENDATIONS.....	41
IX.	REFERENCES	43
X.	ENDNOTES	44

I. ABSTRACT

FDA Mini-Sentinel and CTTI (the Clinical Trials Transformation Initiative) participants jointly assessed the potential for conducting randomized trials in the Mini-Sentinel environment. The goal of the work described here was to assess the capability and willingness of Mini-Sentinel's 18 health plan Data Partners to collaborate in a variety of types of randomized trials, using the Mini-Sentinel Distributed Dataset and the health plans' personnel and infrastructure to:

- Participate in protocol development,
- Identify potential trial participants, using routinely collected electronic information about members' medical history, past and current treatment, medical providers, and coverage;
- Facilitate a trial's implementation, through outreach to providers, direct-to-patient engagement, or through policy measures, such as changes in benefits;
- Assess outcomes, using routinely collected electronic information.

These considerations were applied to three use cases:

- The IMPACT-AF trial, a proposed practice -level educational intervention directed at both primary care clinicians and patients to improve the use of anti-coagulation for atrial fibrillation;
- The Effectiveness of Discontinuing bisphosphonates (EDGE) trial, an individually randomized trial of discontinuation of alendronate therapy by current users;
- The Torsemide Risk Reduction versus Furosemide in Cardiac Insufficiency (TERRIFIC) trial, considered here as a practice or higher level cluster randomized trial.

These potential uses were considered in the context of information developed through a structured questionnaire completed by 16 Mini-Sentinel Data Partners, and also evaluated by the Mini-Sentinel Privacy Panel and patient representatives. This information included an assessment of the Data Partners' capabilities, history of participation in randomized trials, challenges to participation, potential solutions, and interest in participation in such trials.

Data Partners reported substantial prior experience conducting research, including randomized trials. Most had capacity to partner in conducting additional trials. Willingness to participate was conditional on specific trial topics being considered a priority to the Data Partners and their providers, as well as the trial's specific needs, competing demands for personnel and other resources, and adequate financial support.

The Privacy Panel addressed implementation of randomized trials as part of independent research activities sponsored by external sponsors, assessing the requirements of the Common Rule and the Health Insurance Portability and Accountability Act (HIPAA).ⁱ It also addressed the possibility of implementation through a partnership between an external partner and FDA, via analysis of the provisions of the FDA Amendment Act of 2007 (FDAAA).

The overall conclusion of this activity is that Mini-Sentinel Data Partners have considerable and relevant experience to use the resources created by the FDA Mini-Sentinel pilot project to conduct randomized trials. Their interest in participating as partners in developing and implementing these trials depends on a variety of factors, some related to the structure of their organizations and others to the specifics of individual trials. Privacy and legal considerations are not more serious impediments to such partnerships than is true for conventional clinical trials. Analysis and compliance with the HIPAA Privacy Rule and Common Rule are fairly straightforward. In addition, analysis of language contained in FDAAA suggests the possibility that the FDA has authority to facilitate partnerships between FDA and private sponsors that might enable some aspects of such trials, especially regarding the use of information developed as part of the Mini-Sentinel Distributed Database.

II. EXECUTIVE SUMMARY

A. INTRODUCTION

The Mini-Sentinel's 18 health plan Data Partners are potential partners and their Distributed Databases are potential resources to facilitate recruitment and follow-up of participants in randomized trials. Conceptually, hundreds of thousands of individuals (or more) within the Mini-Sentinel Distributed Database (MSDD) may meet the entry criteria for a given clinical trial, yet the use of a distributed research network is often overlooked for identifying, recruiting and following up with these individuals. The MSDD could serve as a foundation for clinical trials by facilitating participant identification, recruitment, and follow-up as well as ascertaining key clinical outcomes. Existing relationships with the Mini-Sentinel Data Partners and infrastructure, the Mini-Sentinel Distributed Database, have the potential to reduce many barriers to trial performance and to facilitate the conduct of pragmatic clinical trials at lower cost, and higher operational efficiency. In the following sections, a framework for considering clinical trials using the Mini-Sentinel Distributed Database is described along with ideal trial characteristics and example use cases that could largely be started in the near term.

There are several types of clinical trial protocols that could be conducted through the MSDD. The choice of individual or cluster randomization depends on the type of intervention, whether or not patient-level consent or other specific patient-level procedures will be required, as well as other factors. Several existing examples of successful cluster and individual randomized trials illustrate the benefit of embedding clinical trials in health care organizations.

B. OPERATIONAL CHARACTERISTICS AND CONSIDERATIONS FOR RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE

Several steps are considered regarding common operational procedures for a trial. Overall, the characteristics that make the Mini-Sentinel environment a favorable one for randomized clinical trials include:

- Objectives relevant to health plans / delivery systems, and, if providers are important to execution, to them
- Engagement of health plans and, where relevant, providers
- Broad study population
- Easily applied interventions
- Measurable clinical outcomes
- Focused safety surveillance

C. BROAD THEMES NECESSARY FOR SUCCESS

Several features are essential to successful partnership between clinical trial sponsors and Mini-Sentinel Data Partners. These include the following:

1. Stakeholder engagement

Clinical trials conducted in partnership with Mini-Sentinel Data Partners will by necessity address topics of interest to the health insurance plans and/or their health delivery systems. It will be important during protocol planning to a) assess the relevant existing research and practice environment at each Data Partner and b) ensure the appropriate stakeholder engagement and approval so that the intervention integrates with the health delivery system or insurance plan. The protocol planning timeline should allow for several levels of engagement. Mini-Sentinel Data Partners each have active research programs and investigators independent of Mini-Sentinel organization within the Data Partner; these may be leveraged for trials using the MSDD.

Engagement of patients or physicians may also require health insurance plan and/or delivery system approvals. Any project that involves direct communication with health insurance plan members must also be approved by a department responsible for member communications. Most protocols will require physician engagement to support the conduct of a trial, the level of which will depend on the intervention. However, the most successful protocols would likely avoid impeding physician workflow by using delivery system or dedicated clinical trial personnel to support study specific activities.

It will be important to educate Data Partners on the variety of study designs that may be used for randomization. Education about cluster randomization is an important stakeholder engagement topic that is not specific to any individual use case or Data Partner. As indicated in the survey results, there is less familiarity and experience with cluster randomization among the Mini-Sentinel Data Partners. Research has suggested that plan leaders and other stakeholders would benefit from information and discussion about this type of design.^{1,2}

2. Defining clusters for cluster randomized designs

Options for clusters include employer or health insurance plan sponsor, practice sites, providers or a geographic region. Data Partner organization are a closed health delivery system can randomize practices or providers more readily than Data Partner organizations that are health insurance plans within the open

health system when a single practice or provider may see patients with multiple health insurance plans. For example, a single medical office sees patients insured by several different health insurers.

3. Centralized informed consent

Centralizing informed consent would be desirable for efficient trial designs. Centralized trial operations subcontractors can be arranged through a Business Associate Agreement or other legal document.

4. Patient and provider participation and communication

Most trials involve some type of patient and provider communication. Mini-Sentinel Data Partners can contact patients and providers. Some potential approaches are described.

5. Patient follow-up data

Membership churn in the health insurance plan Data Partner may make long-term studies (three years or more) infeasible, unless supplemental methods of follow-up are developed.

D. USE CASES FOR POTENTIAL STUDIES WITH A DISTRIBUTED DATABASE

Three use cases are illustrated. Important steps that are routinely part of a trial are also highlighted based on the following areas:

- Screening/Baseline Evaluation
- Provider/Patient Contact and Communication
- Informed Consent
- Randomization
- Treatment Intervention
- Follow-up
- Outcomes ascertainment
- Safety Surveillance/Adverse Events

1. Use Case #1: Strategy/Practice based: IMPACT-AF Clustered Randomized Trial (proposed by Christopher Granger, MD, and colleagues)

Primary Aim: To determine whether a multilevel educational intervention will increase the rate of initiation of oral anticoagulants among patients with atrial fibrillation.

Study Design: Prospective, 2-arm cluster randomized control trial.

Study Population: Patients 18 years and older with atrial fibrillation and at least one CHADS₂ (congestive heart failure, hypertension, age > 75 yrs, diabetes, stroke or TIA) risk factor or at least two CHA₂ DS₂ VASc (congestive heart failure, hypertension, age, diabetes, stroke or TIA, vascular disease, female) risk factors.

We believe these diagnoses and conditions can be identified sufficiently accurately in the Mini-Sentinel Distributed Dataset to support this study.

Study Intervention: This educational intervention will include a toolkit that contains education materials for patients regarding the role of anticoagulation and the benefits and risks of anticoagulation, including options. Physicians will receive feedback reports regarding the rate of anticoagulation among eligible patients benchmarked to other providers in the study. Patients in the intervention arm also receive a report mailed by their health insurance plan Data Partner regarding their risk for stroke and their current anticoagulation status, along with a recommendation, if necessary, to discuss this information with their clinician. Their clinicians will be notified of this report and its contents. This type of direct-to-patient notification as part of a cluster randomized trial was used in a trial to increase adherence to beta-blockers after acute myocardial infarction.³

Outcomes assessment: Outcomes will be assessed using administrative claims and pharmacy claims during the 12 months after randomization.

Sample Size Considerations: A sample size of 40 clusters with an average of 70 subjects per cluster is proposed.

2. Use Case #2: Effectiveness of Discontinuing bisphosphonates (EDGE; proposed by Jeffrey Curtis, MD, MS, MPH)

Primary Aim: The study will evaluate the impact of a continuation versus discontinuation of alendronate on non-vertebral fracture.

Study Design: This study is an intent-to-treat, open-label, 2-arm randomized control trial. Alendronate users would be randomized to alendronate continuation versus discontinuation. Outcomes will be ascertained through administrative claims.

Study Population: The eligible member pool will consist of participants who have been on alendronate for \geq three years.

Study Intervention: Participants will be individually randomized to continuation versus discontinuation of alendronate.

Outcomes assessment: Outcomes will be assessed through administrative claims. The primary outcome would be non-vertebral fracture rates three years after randomization. Secondary outcomes would include hip fractures, osteonecrosis of the jaw, esophageal cancer and atypical femoral fracture.

Sample Size Considerations: A sample size of 8500 patients is proposed.

3. Use Case #3: The Torsemide Risk Reduction versus Furosemide In Cardiac Insufficiency Trial (TERRIFIC; proposed by Eric Velazquez, MD, and colleagues)

Primary Aim: Compare the treatment strategy of torsemide versus furosemide on clinical outcomes in heart failure patients at high risk for clinical events.

Study Design: Prospective, unblinded 2-arm cluster randomized trial of heart failure patients. Practice sites or health insurance plan employers/sponsors will be randomized in a 1:1 fashion to have patients with newly diagnosed heart failure who receive a new prescription for a loop diuretic (either furosemide or equivalent dosing torsemide). Follow-up will consist of routine clinical care and outcomes will be assessed through beneficiary claims.

Study Population: The study population will consist of male and female patients (≥ 18 years old) with a new diagnosis of heart failure and new initiation of a loop diuretic (regardless of ejection fraction).

Study Intervention: Practice sites or health insurance plan employers/ sponsors will be randomized to either oral torsemide or oral furosemide at equivalent doses.

Outcomes Assessment: All study patients will be followed on a usual care basis. Events will also be captured from hospitalization data and survival based on office visits, beneficiary status.

Sample size: A sample size of 6200 patients is proposed

E. CAPABILITIES AND INTEREST OF THE MINI-SENTINEL DATA PARTNERS

Sixteen Data Partners provided information in response to a structured questionnaire which probed the following areas:

1. Previous experience

Fifteen Data Partner organizations had participated in a randomized trial in which individual patients were randomized, and 10 had participated in a trial in which clinicians or clinician organizations were randomized. The most common types of trials were of educational messages, diagnostic tests or procedures, and therapies. Most had identified eligible patients from claims, billing, or laboratory results data, from electronic medical records, via research coordinators or nurses, and through a disease or case management system. All had contacted potential subjects.

2. Willingness to participate in trials using the Mini-Sentinel infrastructure

Seven Data Partners indicated their organization is interested in participating in randomized clinical trial research, the remainder responded "Maybe."

Most respondents identified the following factors as important to a decision to participate in an adequately funded, IRB-Institutional Review Board (IRB) approved trial:

- staff capacity,
- funding reimbursement that adequately covers work,
- organizational structures in place,
- type of work required,
- topic of the research,
- ethical concerns about project,
- risk of protected health information (PHI) disclosure, and
- risk of violating CMS rules about Medicare/Medicaid insurance delivery.

3. Organizational and infrastructure needs

Most respondents indicated that organizational or infrastructure changes would not be needed to support adequately resourced randomized trial activities.

4. Identifying potential subjects

All respondents reported having existing mechanisms for obtaining laboratory data. Ten reported an existing mechanism for a research coordinator or nurse in a clinical department to identify eligible patients. Eight respondents indicated established mechanisms for using disease or case management system data, registry data, surveys and questionnaires, and Internet or social media. Respondents most commonly indicated that substantial barriers for identifying eligible patients exist with internet/social media.

5. Identifying and engaging relevant clinicians

All organizations, but one, reported the ability to identify clinicians who could potentially be involved in a trial. However, four expressed hesitancy and indicated that extra approvals would be needed. For those who were able, most indicated they would work directly with the clinicians and three explained they would refer clinicians to the researchers.

6. Contacting potential subjects

All organizations, but one, are able to obtain patient contact information. All organizations can contact patients by mail or telephone, nine by email, eight by internet/social media, and four by other methods (in person or a portal such as EpicCare's myChart).

7. Using the Mini-Sentinel Distributed Database for exposures and outcomes

Data sufficient to identify many exposures and outcomes are currently contained in the Mini-Sentinel Common Data Model. Nine respondents indicated there would be constraints to using these data for research, six thought there would be no constraints and one did not know. IRB approval and patient consents were the most commonly cited constraint, and one indicated business interests as a constraint. Five Data Partners thought there would be no challenges to following patients and their exposures and

outcomes over time, 11 identified problems when patients change health plans, and one reported that providers or plans do not permit use of diagnosis or procedure codes for research.

8. Obtaining full-text medical records

Charts are currently obtained to validate exposures and outcomes in Mini-Sentinel protocols. Eleven Data Partners said that their organization was as likely to obtain medical records for research as for the public health protocols.

9. Summary of Data Partners' experience, capability, and willingness to participate in randomized clinical trials.

There appears to be cause for optimism about using the Mini-Sentinel infrastructure to facilitate patient recruitment and follow-up of participants in randomized trials. One area that seemed more challenging for some Data Partners was engaging clinicians, especially if a protocol required a more time-consuming role from them such as discussing participation in a trial, obtaining informed consent, performing randomization or implementing interventions. Many Mini-Sentinel Data Partners had a high degree of experience with most aspects of individually randomized trials and there was a general overall willingness to consider participating in randomized trials using the Mini-Sentinel infrastructure.

A surprising finding was that when asked about specific roles, respondents seemed less willing and able to engage in such trials. One possible explanation for this seeming paradox may be that respondents did not feel they could commit to being willing or able without more information and resources. The large number of factors that respondents indicated would be important to consider before deciding whether to participate suggests that this may be the case.

F. DATA PRIVACY CONSIDERATIONS

HIPAA permits Data Partners to access PHI in their records, and to contact healthcare providers caring for their members, in order to gather information in preparation for research and to recruit patients for participation in clinical trials, without need to first obtain authorization from those patients. HIPAA also permits Data Partners to access PHI for research purposes; however, prior patient authorization is required unless it is waived by an IRB. Disclosing de-identified data or a limited data set for research purposes does not require patient authorization.

Data Partners covered by the Common Rule will need informed consent prior to using identifiable information from patients for either research preparation, recruitment or the conduct of research, unless such consent is waived by an IRB. The Common Rule does not apply to data that is not identifiable to a researcher.

FDA has the authority to determine if any of the proposed use cases for the MSDD can be conducted pursuant to FDAAA. Studies conducted under the authority of FDAAA will be treated as public health uses of the MSDD and the provisions governing research in HIPAA and the Common Rule will not apply.

G. OVERALL CONCLUSIONS

There are substantial opportunities to improve the efficiency of clinical trial recruitment and implementation through partnerships with Mini-Sentinel Data Partners. Such trials will require alignment with the interests of the Data Partner organizations and their providers, and will involve planning activities that are not part of the development of traditional clinical trials. However, these additional steps may allow other activities to be performed more quickly and at lower total cost than conventional methods for identifying, enrolling, and following clinical trial participants. Neither the Common Rule nor HIPAA provisions prevent implementation of such trials. In addition, under FDAAA, it may be possible for FDA to enter into partnership with private sponsors to facilitate some aspects of using the data developed by the Mini-Sentinel program.

A potential next step could be to assess the potential eligible population for the three use cases, or for other potential trials of interest.

III. INTRODUCTION

Despite the surge in clinical trials, there remain frequent gaps in the knowledge base for common conditions regarding the risks and benefits of routine treatments and strategies of care.⁴ Lengthy and burdensome processes for the conduct of clinical trials have led to a costly and inefficient clinical trial enterprise that limits the ability to close these knowledge gaps.⁵ These burdens have also led to the redistribution of clinical research globally,⁶ and have decreased the overall participation of centers and patients in the United States.⁷ It will be advantageous to minimize these barriers.⁸

The MSDD is a potential infrastructure to facilitate recruitment and follow-up of participants in randomized trials. Conceptually, hundreds of thousands of individuals within the MSDD may meet the entry criteria for a given clinical trial, yet the use of a distributed research network is often overlooked for identifying, recruiting and following up with these individuals. The MSDD could serve as a foundation for clinical trials by facilitating participant identification, recruitment, and follow-up as well as ascertaining key clinical outcomes. Using existing infrastructure, the MSDD has the potential to circumvent the major barriers of trials and facilitate the conduct of pragmatic clinical trials at lower cost, and higher operational efficiency. In the following sections, a framework for considering clinical trials conducted in partnership with the Mini-Sentinel Data Partners using the Mini-Sentinel Distributed Database is described along with ideal trial characteristics and example use cases that could largely be started in the near term.

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA). Its mission is to create capabilities to monitor the safety of marketed medical products using routinely collected electronic health data. Its resources include a distributed dataset containing electronic healthcare data from 18 health insurance plans and the infrastructure to maintain the distributed dataset within each of the 18 health plans—referred to henceforth as “Data Partners.”

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership established by the FDA and Duke University. Its mission is to identify and promote practices that will increase the quality and efficiency of clinical trials. CTTI is now comprised of more than 60 organizations from across the clinical trial enterprise.

Mini-Sentinel, CTTI, and FDA collaborated in an activity assessing the feasibility of using the MSDD health insurance to facilitate recruitment and follow-up of participants in randomized trials, including both individual and cluster randomized trials.

This white paper is a synthesis of the working group's examination of the feasibility of using the MSDD to facilitate recruitment and follow-up of participants in randomized trials, including both conventional individually randomized and cluster randomized trials. The working group's evaluation is split into three domains of policies and procedures, data, and privacy: a) Data Partner experience and capability to conduct research studies; b) potential clinical trials frameworks and use cases that may be plausible within Mini-Sentinel; and c) privacy considerations for uses of the MSDD beyond surveillance.

The clinical trials evaluation explores both the plausibility and logistics of utilizing Mini-Sentinel data to collect selected outcome data, including both endpoints and adverse events. The working group dissected three potential trial cases for use in conjunction with the Mini-Sentinel Distributed Database. These use cases evaluate a variety of clinical trial design scenarios, including both individual as well as cluster randomized trials, and assess the feasibility of implementing these various designs within individual Mini-Sentinel Data Partner organizations.

The data section considers whether Data Partners could use their Mini-Sentinel distributed databases to identify potential participants in research studies, then lead or facilitate enrollment of these individuals, and finally, whether they can use their datasets to perform some or all of the outcome assessment. A survey of Mini-Sentinel's Data Partners revealed a high degree of prior research experience among respondents as well as enthusiasm for this concept; however, there was significant disparity between experience and willingness and ability to participate.

The paper concludes with an assessment of privacy law and policies related to the use of Mini-Sentinel resources for these research activities, rather than public health practice. Specifically, this section addresses ethical and practical issues related to randomization in research, including 1) issues related to use of data to identify patients for recruitment, 2) IRB oversight, 3) approaches to obtaining informed consent, 4) use of data from the Mini-Sentinel Distributed Database to conduct research (as opposed to public health surveillance), and 5) oversight and administration of clinical research, in addition to IRB review.

This paper provides baseline policies and procedures for conducting research studies within the Mini-Sentinel system. Future development work will need to focus on finding practical and efficient implementation strategies that also appropriately balance ethical, as well as privacy requirements within the clinical trials arena.

IV. EVALUATING THE POTENTIAL FOR CONDUCTING RANDOMIZED TRIALS IN PARTNERSHIP WITH MINI-SENTINEL DATA PARTNERS

Partnership with Mini-Sentinel data contributors (referred to as “Data Partners”) to conduct randomized trials using Mini-Sentinel data resources will require robust collaborations that align the interests of research sponsors with the health insurance plans, engage stakeholders at several levels, create processes for both identifying potential candidates for a prospective study and, for some trials, working with patients’ clinicians to contact appropriate candidates. Follow-up through the distributed database will require mechanisms to capture exposures, events and outcomes using existing automated data and to utilize Mini-Sentinel’s processes for obtaining and reviewing full text records. Appropriate policies and procedures to allow technical implementation, oversight, and engagement of potential participants must be developed for trials that employ conventional approaches to randomization as well as for those that use cluster randomization strategies. Three working groups addressed 1) characteristics of randomized trials that might be of interest and suitable for implementation by the Mini-Sentinel Data partners, 2) data partner participation, and 3) regulatory issues related to this activity.

V. CLINICAL TRIALS SUBGROUP REPORT: FRAMEWORK AND POTENTIAL USE CASES

A. CHARACTERISTICS OF PROTOCOLS FOR DISTRIBUTED RESEARCH NETWORK

Several types of clinical trial protocols could, in principal, be conducted through the Mini-Sentinel Distributed Database. **Table 1** highlights the general phenotypes of trials.

The choice of individual or cluster randomization depends on the type of intervention, whether or not patient level consent or other specific patient-level procedures will be required, as well as other factors. Several existing examples of successful cluster and individual randomized trials illustrate the benefit of embedding clinical trials in health care organizations.

For cluster design studies, the unit of randomization may be practice sites, hospitals, health insurance plans or sponsor of beneficiary (i.e. employer, union, association). In the case of the trials leveraging the MSDD, the selection of randomization of health insurance plans or practice sites depends on the type of intervention and the ability to efficiently randomize the cluster.

An example of a health insurance plan based cluster randomization of patients is the MI FREE MI trial.⁹ In this study, the randomized assignment occurred at the level of the insurance-plan sponsor (i.e., employer, union, government or other association that sponsors the benefits package). In this trial, patients were identified through hospital discharge health insurance claims after myocardial infarction and randomly assigned with their insurance-plan sponsors to full prescription coverage (1494 insurance-plan sponsors with 2845 patients) or usual prescription coverage (1486 insurance-plan sponsors with 3010 patients) for all statins, beta-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin-receptor blockers.

Potentially eligible patients were identified using administrative discharge claims submitted to the health insurance plan; subsequent follow-up for clinical events, as well as medication adherence, was done through beneficiary claims. The trial showed the elimination of copayments for drugs prescribed after myocardial infarction did not significantly reduce rates of the trial's primary outcome of first major vascular event or revascularization. However, enhanced prescription coverage improved medication adherence and rates of first major vascular events and decreased patient spending without increasing overall health costs.

A hospital based cluster randomization study of three strategies to prevent methicillin resistant *Staphylococcus aureus* clinical isolates in ICUs by Huang et al. highlights a treatment intervention. In this study, all ICUs in 43 hospitals were randomly assigned to the same strategy.¹⁰ The final population of the study included over 70,000 patients and the final results showed universal decolonization to be the most effective strategy. Cluster randomization, combined with use of routinely collected electronic health data, allowed great efficiencies, permitting the study to be completed at a cost of approximately \$40 per patient.

An example of individual patient randomization is a clinical trial of telephone-care management.¹¹ In this study, over 174,000 subjects were identified through insurance claims; those identified with high risk medical conditions or predicted high health care costs were randomly assigned to either usual-support group or an enhanced-support group that instructed subjects about shared decision making, self-care, and behavioral change. The primary outcome measures included one year total medical costs and number of hospital admissions as assessed through insurance claims. Importantly, since this was a quality improvement study, the study was deemed exempt and granted a waiver of informed consent. The final results showed that a targeted telephone care-management program was successful in reducing medical costs by 3.6%--driven largely by a reduction of 10% in annual hospital admissions.

Ideal characteristics for conducting trials in partnership with Mini-Sentinel Data Partners include pragmatic designs that are integrated easily within clinical care. Patient populations should be easily identifiable with minimal to no exclusion criteria. The ability to efficiently include patients can be expedited by a lack of burdensome trial procedures and monitoring requirements. Ideally, follow-up and outcome ascertainment should be achievable through the data routinely collected in clinical practice and study timeframe less than 3 years.

In the current model of Mini-Sentinel, studies that are intended to support a label extension or a new indication are more challenging to implement. Potential issues for studies performed under Investigational New Drug (IND) provisions include compliance with current regulatory processes such as reporting of serious adverse events, and assurances for investigator responsibilities. Compliance with 21 CFR part 11 would also be difficult to implement through normal health plan processes. Therefore, the focus of clinical trials most aligned with the Mini-Sentinel framework are highlighted below. Strategies to implement IND trials and the necessary compliance with 21 CFR part 11 are out of scope for this document.

Table 1. Clinical Trial Phenotypes

	STUDY TYPE	DESIGN	POPULATION/SITE	INTERVENTIONS	BLINDING	OUTCOMES	EXAMPLES	FEASIBLE
1	Strategy or Clinical Practice Trial **	Cluster-level	Health plans, 100s of sites >10,000 pts	Clinical practice strategies	Un-blinded	Clinical outcomes	Decolonization to Prevent ICU Infection	Yes
2	Pre-approval Drug	Cluster-level	Health plans, 100s of sites >10,000 pts	Drug A vs. Control	Blinded	Clinical and patient reported outcomes	Drug in Phase III	Defer
3	Non-IND cluster trials**	Cluster-level	Health plans, 100s of sites >10,000 pts	Drug A, B, C, D	Un-blinded	Clinical outcomes	Any drug (e.g. bisphosphonates, anti-hyperglycemics)	Yes
4	Strategy or Clinical Practice	Patient-level	<200-300 sites 10-1000s pts <10,000	Clinical practice strategies	Un-blinded	Clinical outcomes	Target glycemic control; disease management	Yes
5	Pre-approval Drug	Patient-level	10-1000s pts <10,000	Drug A vs. B	Blinded or Un-blinded	Clinical and patient reported outcomes	Drug in Phase III	Defer
6	Non-IND individual trials**	Patient-level	10-1000s pts <10,000	Drug A vs. B	Blinded or Un-blinded	Clinical outcomes	Any drug (e.g. diuretics, hyperglycemics)	Yes

**** Ideal Mini-Sentinel Distributed Database Use Cases**

B. OPERATIONAL CHARACTERISTICS AND CONSIDERATIONS FOR RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE

Characteristics that make a trial most suitable for the Mini-Sentinel Data Partners and Distributed Database include:

Pragmatic objective—Study designs with a goal of addressing treatment decisions under usual or routine clinical conditions that integrated with practice.

Provider integration—for interventions that involve providers (i.e., hospitals, physicians, other health care delivery or therapeutic venues), having provider ‘buy-in’ for approaching patients and applying a randomized intervention are critical for success. Assessment of provider participation could range from assent for approaching patients to participation in trial procedures or interventions.

Broad study population—Inclusion of subjects to be eligible similar to those encountered in daily clinical practice allows better evaluation of the heterogeneity of effects as well across diverse populations than do clinical trials with narrow eligibility criteria.

Easily applied interventions—Open-label regimens with flexible dosing and practice strategies that are among the potential options for a given practice are important attributes. While blinding is customarily considered the most rigorous method to prevent bias, it leads to significant limitations on interventions in the care setting. In many cases, blinding may be either impractical or unnecessary, especially in cases when the outcomes are ascertained in a blinded fashion.

Commonly available clinical outcomes—Outcomes that are defined by normal health care delivery or services most often captured through claims. In some cases, other routine surveillance of outcomes might be used.

Post-marketing assessments—There are advantages to studies that focus on postmarketing evaluation of safety and effectiveness. These trials may be more likely to be of interest to Data Partners, and they may also require less regulatory oversight if they are exempt from regulations covering Investigational New Drugs (INDs). Criteria for IND exemption are outlined in CFR 312.2(b) which stipulates the trial is exempt if the trial 1) is not intended to support a new indication or change in labeling, 2) is not intended to support a change in advertising, 3) does not involve a new route of administration or dosage level or use in a patient population or other factor that significantly increase the risks associated with the product, 4) is conducted in compliance with requirements for institutional review and informed consent, 5) follows rules regarding promotion of investigational drugs.

C. NECESSARY CENTRALIZED EFFICIENCIES FOR RANDOMIZED CLINICAL TRIALS IN THE MINI-SENTINEL DISTRIBUTED DATABASE

In addition to operational characteristics for specific protocols, there is a broad need for approaches to centralized activities such as IRB review to optimize efficiency of trials within Mini-Sentinel. Broad themes necessary for success include the following:

1. Stakeholder engagement and approvals

Clinical trials conducted in partnership with Mini-Sentinel Data Partners will, by necessity, address topics of interest to the health insurance plans or health systems. In part, because of this high relevance, it will be important during protocol planning for each Data Partner and their unique stakeholders to consider how the study can both a) assess the relevant existing research and practice environment at each Data Partner and b) ensure the appropriate stakeholder engagement and approval so that the intervention meshes with the delivery system or health insurance plan. Some Data Partners require that an internal investigator be included as a co-investigator.

The protocol planning timeline should allow for acquisition of stakeholder approval involving several levels of engagement. The Mini-Sentinel Data Partners each have active research programs and

investigators; these may be leveraged for trials using the Mini-Sentinel Distributed Database. To minimize overlap, it will be important to determine what related research Data Partners are already conducting. Furthermore, existing practice guidelines and policies within the Data Partner organizations must be explored for conflict. Several Data Partner organizations have a guidelines committee, treatment algorithms group, and/or a Pharmacy and Therapeutics committee that may require reviewing the study prior to Data Partner participation.

Engagement of patients or physicians may also require Data Partner approvals. Any project that involves direct communication with patients must also be approved by some type of member communications department. Most protocols will require physician engagement, the level of which will depend on the intervention. Of note, the provider relationships for Data Partners who are national health insurance plans are different from Data Partners who are closed health systems. As such, national health insurance plans may have a lower provider response rate given the variable penetrance of a national health insurance plan's products across physician practices. For example, one national health insurance plan shared an example of a quality improvement intervention in which physician practices were faxed patient lists and asked to indicate which patients could be contacted for the intervention (there was an option to approve all, none, or mark the individual patients they approved). The physician practice response was about 20%, highlighting the need to carefully consider how to engage physicians about a study through incentives or other means.

It will be important to educate Data Partners on the variety of study designs that may be used for randomization. Education about cluster randomization is an important stakeholder engagement topic that is not specific to any individual use case or Data Partner. As indicated in the Data Partner survey results (Section: Data Subgroup Report), there is less familiarity and experience with cluster randomization among the Mini-Sentinel Data Partners. Prior research has suggested that health insurance plan leaders and other stakeholders need education in order to achieve buy-in with this type of design.^{1,2}

2. Defining clusters for cluster randomized designs

Data Partners, which are health delivery systems, can randomize practices more readily than open health systems when a single provider may see patients with multiple health insurance plans (e.g. seeing patients with Humana and Aetna insurance within a single medical office). One solution may be to limit any particular geographical region to a single participating Data Partner based on factors, such as Mini-Sentinel patient volume in the region. Another approach would be randomization at the insurance-plan sponsor/ employer level. Data Partners would submit a file with each beneficiary's Mini-Sentinel ID number and a cluster indicator for each patient, e.g. either geographic or employer ID. Some employers offer multiple health insurance-plans, so these employers might need to be excluded.

3. Centralized informed consent

Centralizing informed consent would be desirable for efficient trial designs. Although some Data Partners have their own staff who can administer informed consent, centralized informed consent would also be

possible. Attitudes toward centralizing the informed consent process vary across Data Partners and in some cases it may not be allowed or is allowed only with specific circumstances/requirements. This could cause substantial delay to operationalize at these few Data Partners. Centralized trial operations subcontractors would need to submit proof of human subjects training and be required to follow any Data Partner rules. A Business Associate Agreement or other legal document would be needed before identifiable member information could be transferred.

4. Patient and provider participation and communication

Most cases or scenarios will involve some type of patient and provider communication, and Mini-Sentinel Data Partners can contact patients and providers. Depending on the intervention and whether individual informed consent would be required, various approaches could be used. For example, if a patient's treatment will be changed or a new treatment will be introduced in a randomized fashion, obtaining explicit physician agreement may be required. Some potential approaches that could be considered for use (in which both providers and patients would be contacted) are described below.

Approach 1: (Data Partner contacts patient, patient responsible for confirming with provider) Under this approach, the Data Partner identifies patients and their physicians and provides them with the study information. The letter to the patient includes the comment that they should contact their provider to find out if the study is right for them, and offers to send the patient's contact information to the External Research Sponsor. The Data Partner would also provide information about the research to the provider along with a list of their patients that may be eligible and who received the study information. Once a patient agrees to be contacted, the Data Partner sends the patient and provider information to the External Research Sponsor. The External Research Sponsor does the informed consent, study eligibility, randomization, and intervention.

Approach 2: (Data Partner contacts patient, patient confirms with provider, patient contacts External research sponsor) An alternative opt-in process is that the patient contacts the External research sponsor directly and the External research sponsor provides documentation of patient consent for the Data Partner to share patient data with the External research sponsor. The patient would be responsible for confirming with the provider that the study is right for them. The provider would be given notification of their patients' potential eligibility and that the Data Partner sent a letter to patient.

Approach 3: (protocol requires provider approval prior to patient contact) Under this approach, the Data Partner would first send notification to providers of their patients' potential eligibility for the study. This would include a list of patients with a place to mark (yes/no) their approval with a deadline for the provider to return the completed form. For the patients approved by their provider, the Data Partner would send study information to the patient with the comment that their provider approved of their participation and with instructions to contact the External research sponsor for more information. The External research sponsor would conduct the informed consent, study eligibility, randomization, and intervention.

Approach 4: (member opt out of Data Partner providing their contact information to the External research sponsor) With this approach, after a patient is approved for study participation by their provider (as in approach 3), the patient would be contacted by the health insurance plan and told that their provider agrees to individual's study participation. The health insurance plan would ask the patient to reply, if they do not want their contact information provided to the External research sponsor. A Data Partner might need to check with legal, compliance, and member communications groups to see if there are any constraints to this approach.

In addition to these methods, it would be possible for the Data Partner to enter into a Business Associate Agreement with a research sponsor to allow the sponsor to perform some of the Data Partner functions described above.

5. Patient follow-up data

For trials that require years of follow-up the rate of disenrollment ("membership churn") may be too great – up to 30% per year for some plans.

D. USE CASES FOR POTENTIAL STUDIES WITH A DISTRIBUTED DATABASE

In the following section, three use cases are illustrated. Important steps that are routinely part of a trial are also highlighted based on the following areas:

- Screening/Baseline Evaluation
- Randomization (Individual or Cluster)
- Treatment Intervention
- Follow-up
- Outcomes ascertainment
- Safety Surveillance/Adverse Events

1. Use Case #1: Strategy/Practice based: IMPACT-AF Clustered Randomized Trial (proposed by Christopher Granger, MD, and colleagues)

Background and Rationale: Stroke is a leading cause of death in the United States and about one in five strokes is due to atrial fibrillation. Additionally, stroke is the leading cause of disability in adults. Each year, millions of stroke survivors adapt to a life with restriction in activities of daily living as a consequence of this disease. Over two thirds of these strokes can be prevented with oral anticoagulation. A 2007 meta-analysis of antithrombotic therapy use for the prevention of stroke in patients with atrial fibrillation found that treatment with adjusted-dose warfarin reduced stroke risk by 62% (95% confidence interval [CI], 48% to 72%) and demonstrated low rates of major hemorrhage. The newer oral anticoagulants are at least as good as warfarin at preventing stroke, with decreased rates of intracranial hemorrhage. Despite the effectiveness of anticoagulation, recent literature reviews and studies have documented that current practice does not follow published guidelines, resulting in substantial occurrence of preventable ischemic stroke. In a US study, only 50% of eligible elderly patients received anticoagulation. Underuse of

anticoagulation appears to be, at least in part, due to the concern of increased risk of bleeding, especially in the elderly. Few quality improvement interventions have been evaluated to determine impact on patient care and clinical outcomes for patients with atrial fibrillation to reduce stroke rates. Using methods that have been shown to improve adherence including education of healthcare providers, improved communication between physicians and patients, patient education and educational outreach visits, and measuring and providing feedback regarding adherence, this study will test an educational intervention to determine impact on patient care and clinical outcomes.

Primary Aim: To determine whether a multilevel educational intervention will increase the rate of initiation of oral anticoagulants among patients with atrial fibrillation.

Secondary Aim: To determine whether a multilevel educational intervention will increase the persistence of oral anticoagulant use among patients with atrial fibrillation.

Study Design: This study is a prospective, 2-arm cluster randomized control trial. Practice sites or health plan sponsors /employers will be randomized in a 1:1 fashion to either receive enhanced educational intervention versus standard of care. Physicians should be randomized in clusters at least as large as their practices to avoid the potential of crossover effects of the clinician intervention. Health insurance plans should determine the size of the clinician clusters based on their ability to identify primary care clinicians or other clinicians treating atrial fibrillation (i.e. cardiologists) who practice together. In principle, they could decide to randomize by geographic region, e.g., state or metropolitan area.

Study Population: The eligible member pool will consist of patients 18 years and older with atrial fibrillation and at least one CHADS₂ (congestive heart failure, hypertension, age > 75 yrs, diabetes, stroke or TIA) risk factor or at least two CHA₂DS₂VASc (congestive heart failure, hypertension, age, diabetes, stroke or TIA, vascular disease, female) risk factors. All of the diagnoses and conditions noted below can be identified by ICD-9 codes or other readily available information.

Inclusion Criteria:

- Age 18 years or older
- Atrial fibrillation [AF: ICD-9-CM 427.31 or atrial flutter (ICD-9-CM 427.32) was reported on a single inpatient claim or at least 2 outpatient]
- Risk Factor for thromboembolic event:
 - One CHADS₂ (congestive heart failure, hypertension, , diabetes, stroke or TIA by ICD-9; age > 75 yrs) risk factor OR
 - Two CHA₂DS₂VASc risk factors (congestive heart failure, hypertension, diabetes, stroke or TIA, vascular disease by ICD-9; age, female)

Exclusion Criteria:

- Mechanical prosthetic valve

- History of life-threatening bleeding (intracranial hemorrhage)

Study Intervention: This study is proposed as a cluster randomized trial with interventions directed both at primary care providers and patients. Intervention sites will have enhanced educational activities targeted to the primary care providers or other health care professionals involved in the care of patients with atrial fibrillation. The educational intervention will include a toolkit that contains education materials for patients regarding the role of anticoagulation and the benefits and risks of anticoagulation, including options. In the intervention arm, physicians will receive feedback reports regarding the rate of anticoagulation among eligible patients benchmarked to other providers in the study. Patients in the intervention arm also receive a report mailed by their health insurance plan regarding their risk for stroke and their current anticoagulation status, along with a recommendation, if necessary, to discuss this information with their clinician. Their clinicians will be notified of this report and its contents. This type of direct-to-patient notification as part of a cluster randomized trial was used in a trial to increase adherence to beta-blockers after acute myocardial infarction.⁹

Outcomes assessment: Outcomes will be assessed using administrative claims and pharmacy claims submitted to the health insurance plan during the 12 months after randomization.

Sample Size Considerations: Assuming intracluster correlation coefficients (ICC) from 0.001 to 0.05, we will have adequate power to detect the expected 10% difference between intervention and control. With an average cluster size of 40-70 patients per cluster, a randomization allocation ratio of 1:1, and a post-intervention use of oral anticoagulant of 70% with a post-control rate of 60%, there will be roughly 88-95% power with 20 clusters per group with an ICC of 0.02. Therefore, with 40 clusters (that is 2,800 subjects assuming a cluster size of 70 subjects) and ICC=0.02, we will have roughly 97% power to detect 10% improvement and roughly 86% power to detect 8% improvement.

Trial Operational Procedures:

Provider Participation: The goal of the study is improving delivery of care by providers, who will participate by virtue of receiving educational materials and be enabled to use quality improvement tools.

Mini-Sentinel modular programs will be used to obtain preliminary data to identify the rates of initiation and persistence of anticoagulation in the target population for the Data Partner.

New SAS programs, i.e., not part of the current Mini-Sentinel program library, will be required to allow Data Partners to link patients to clinicians, and/or link clinicians to practices.

Highlighted areas:

IRB: It will be necessary to determine whether this research qualifies as a quality improvement program, and thus is exempt from IRB review.

Consent: If there is IRB oversight, it will be necessary for the IRB to determine whether individual informed consent is necessary, and if so, whether consent needs to be obtained from the clinicians and/or the patients.

Notification of participants: It will be necessary to determine whether and how individuals in the clusters are notified of the existence of the trial.

Screening/Baseline Evaluation: Patients eligible for the study will come from those diagnosed with atrial fibrillation based on administrative claims. Other baseline data will also derive from the Mini-Sentinel distributed dataset.

Randomization: The unit of randomization will be determined by Data Partners, with cluster size ranging from and individual practices to the entire health insurance plan. Data Partners will identify the clusters, and link cluster status to individuals' data in the distributed dataset. Randomization will be done centrally by external research sponsor.

Treatment Intervention: The intervention consists of educational materials and tools to describe the risks and benefits to patients regarding anticoagulation among patients with atrial fibrillation. All materials directed at providers and patients would be distributed from the Data Partner.

Drug supply or blinding: N/A

Follow-up: Assessment of events would derive from routine administrative claims submitted by the provider to the health insurance plan or through the medical record of the health care delivery system.

Safety surveillance/pharmacovigilance: N/A

2. Use Case #2: Effectiveness of Discontinuing bisphosphonatEs (EDGE; proposed by Jeffrey Curtis, MD, MS, MPH)

Background and Rationale: Bisphosphonate treatment is commonly used to prevent fractures in patients with osteoporosis. Typically, patients are placed on bisphosphonate therapy for an indefinite duration. Among patients with extended duration, multiple studies have raised safety concerns such as osteonecrosis of the jaw. In addition, there may also be severe suppression of bone turnover and associated atypical fractures. There is minimal evidence on optimal duration of use and consequence of continuing or stopping. Understanding whether patients can be withdrawn from bisphosphonate therapy without any excess fractures would allow a better understanding of the appropriate treatment period.

Primary Aim: The study will evaluate the impact of a continuation versus discontinuation of alendronate on non-vertebral fracture.

Secondary Aims: To compare the rates of hip fractures between continuation versus discontinuation of alendronate and compare the rates of adverse events (osteonecrosis of the jaw, esophageal cancer and atypical femoral fracture).

Study Design: This study is a prospective, intent-to-treat, open-label, 2-arm randomized control trial. Participants would be randomized to alendronate continuation versus discontinuation. Outcomes will be ascertained through administrative claims submitted to the health insurance plan or through medical records from the health delivery system.

Study Population: The eligible member pool will consist of participants who have been on alendronate for \geq three years.

Inclusion Criteria:

- Age 18 years or older at the time of enrollment
- History of osteoporosis
- Have filled prescriptions for alendronate three years to five years.

Exclusion Criteria: None

Study Intervention: Eligible patients who agree to participate in the study will be randomized in a 1:1 ratio to continuation versus discontinuation of alendronate.

Outcomes assessment: Outcomes will be assessed through administrative claims submitted to the health insurance plan. The primary outcome would be non-vertebral fracture rates 3 years after randomization. Secondary outcomes would include hip fractures, osteonecrosis of the jaw, esophageal cancer and atypical femoral fracture.

Sample Size Considerations: The overall estimate of 8% is likely most reasonable for this fracture rate in the continuation group, and a sample size of about 8500 patients total as a base case. Since the primary analysis will be non-inferiority analysis based, the assumption is that the bisphosphonate withdrawal group will have a non-inferiority margin of 2.5% (a value that a panel of experts endorsed).

Trial Operational Procedures:

Screening/Baseline Evaluation: Patients would be identified based on prior administrative claims for osteoporosis and dispensing of alendronate for three to five years. Other baseline data would be derived from the Mini-Sentinel distributed dataset.

New SAS programming by Data Partners will be required to link patients to providers.

Provider Participation: Providers would be contacted, informed and educated about the trial. They would also need to provide permission for patients to participate in the trial and in some practice settings facilitate informed consent.

Consent: We will explore the possibility of using a centralized telephone administered consent process, supplemented by mailed documents and/or internet support.

IRB: IRB oversight will be required.

Randomization: The unit of randomization will be the patient and randomization would occur within a health insurance plan or health delivery practice site. Patients will receive information regarding the study and would complete informed consent for participation.

Treatment Intervention: Once randomized, a patient would either continue on alendronate or discontinue the prescription.

Monitoring adherence to assigned group: Participants' alendronate refill behavior will be monitored. If patients randomized to discontinuation continue to be dispensed alendronate, study personnel will contact the patient and her provider to determine whether this behavior is an intentional departure from the study protocol. For participants who are assigned to continue alendronate, but who discontinue therapy, no effort will be made to encourage them to resume treatment.

Drug supply or blinding: Patients assigned to continue alendronate in open label fashion would continue as prescribed per usual care.

Follow-up: Assessment of events would be determined from diagnosis and procedure codes in the Mini-Sentinel distributed dataset.

Safety surveillance/pharmacovigilance: Routine assessment of clinical events of interest would be done per clinical care. The study is exempt from an IND per CFR 312.2(b): (1) exempts the trial from IND regulations if the trial 1) is not intended to support a new indication or change in labeling, 2) is not intended to support a change in advertising, 3) does not involve a new route of administration or dosage level or use in a patient population or other factor that significantly increase the risks associated with the product, 4) is conducted in compliance with requirements for institutional review and informed consent, 5) follows rules regarding promotion of investigational drugs.

3. Use Case #3: The Torsemide Risk Reduction versus Furosemide In Cardiac Insufficiency Trial (TERRIFIC; proposed by Eric Velazquez, MD, and colleagues)

Background and Rationale: The ACC/AHA guidelines indicate that the optimal use of diuretics is the cornerstone of any successful approach to the treatment of heart failure (HF). Despite preclinical and clinical data supporting benefits with torsemide over furosemide, furosemide is the most commonly used loop diuretic. Small studies and observational studies suggest there are short and long-term benefits of torsemide versus furosemide. Despite this data, furosemide remains the initial diuretic of choice. The only way to address this question is through a large comparative effectiveness trial. There remains an unmet need for a robustly powered, prospective randomized trial to definitively determine whether diuretic therapy with torsemide improves outcomes compared to furosemide in HF patients.

Primary Aim: To compare the treatment strategy of torsemide versus furosemide on clinical outcomes in HF patients at high risk for clinical events.

Secondary Aims: To compare torsemide vs. furosemide with regard to other important clinical endpoints:

- HF rehospitalization rate over one year
- Time to mortality and total CV hospitalizations

Study Design: This is a prospective, unblinded 2-arm cluster randomized trial of 6,200 HF patients. Health delivery practice sites or health insurance plan sponsors/ employers will be randomized in a 1:1 fashion to have patients with newly diagnosed heart failure receive either furosemide or equivalent dosing torsemide. Follow-up will consist of routine clinical care and outcomes will be assessed through administrative claims submitted by providers to health insurance plans.

Study Population: The study population will consist of male and female patients (≥ 18 years old) with a new diagnosis of heart failure and new initiation of a loop diuretic (regardless of ejection fraction).

Inclusion Criteria:

- Age ≥ 18 years
- Hospitalization with a primary diagnosis of heart failure
- Discharged on a loop diuretic of an outpatient dose of oral furosemide (or equivalent) ≥ 20 mg daily

Exclusion Criteria:

- End-stage renal disease requiring renal replacement therapy

Study Intervention: TERRIFIC will randomize health delivery practice sites or health insurance plan sponsors/employers in a 1:1 randomization to either oral torsemide or oral furosemide (note dosing of torsemide compared to furosemide will be 2:1 per routine clinical practice).

Outcomes Assessment: All study patients will be followed on a usual care basis. Events will also be captured from hospitalization data and survival based on presence of office visits or Social Security Death index status.

Sample Size Considerations: Approximately 6200 subjects will provide greater than 90% power to detect a 10% relative (or 5% absolute) reduction in the primary endpoint with torsemide. Accounting for reasonable estimates of drop-in, drop out, loss to follow up and cross-over, and an intra-class correlation of 0.01.

Trial Operational Procedures:

Provider Participation: Providers would be contacted and informed about the trial. Since the unit of randomization will be at a cluster, Data Partners will need to decide whether the clusters (practices or larger groups) will have the ability to choose to participate in the trial. For clusters that do participate, providers would need to be informed that their practice site could be randomized to furosemide or torsemide. The most appropriate mechanism for the practice (cluster) would be used to remind clinicians of the preferred diuretic. This might be through formulary management, through interactive prescribing guides, e.g., EpicCare Best Practice Alerts, or other mechanism. Clinicians will have the ability to prescribe the agent of their choice.

A mechanism will need to be developed to inform patients of the study, and their ability to opt out and have their clinicians prescribe without reference to the cluster assignment.

Informed consent: It will be necessary to address consent at the level of the prescriber cluster and the patients in the cluster.

New SAS programming by Data Partners will be required to link patients to providers.

Screening/Baseline Evaluation: Subjects would be identified after the fact based on administrative claims for heart failure and new prescription claims for furosemide or torsemide. Other baseline data would be derived from enrollment and demographic data in the Mini-Sentinel Distributed Dataset.

Randomization: The unit of randomization will be health insurance plan sponsors/ employers or health delivery practice sites and done centrally.

Treatment Intervention: Once randomized, a cluster would be allocated to a recommendation, formulary preference, or prescription tiering preference of furosemide or equivalent dosing of torsemide.

Drug supply or blinding: Patient assignment to furosemide or torsemide would be done in an open-label fashion. Physicians would have the option of switching based on clinical need.

Follow-up: Assessment of events would derive from administrative claims submitted by providers to health insurance plans or through the medical record of the health care delivery system.

Safety surveillance/pharmacovigilance: Routine assessment of clinical events of interest would be done per clinical care. The study is exempt from an IND per CFR 312.2(b): (1) exempts the trial from IND regulations if the trial 1) is not intended to support a new indication or change in labeling, 2) is not intended to support a change in advertising, 3) does not involve a new route of administration or dosage level or use in a patient population or other factor that significantly increase the risks associated with the product, 4) is conducted in compliance with requirements for institutional review and informed consent, 5) follows rules regarding promotion of investigational drug.

VI. DATA SUBGROUP REPORT: MINI-SENTINEL RANDOMIZATION WITHIN THE MINI-SENTINEL DISTRIBUTED DATABASE

The project's Data Subgroup examined the feasibility of using the Mini-Sentinel infrastructure to facilitate patient recruitment and follow-up of participants in randomized trials.

A. METHODS

A Data Partners Survey was developed by the project's Data Subgroup and CTTI staff. Please refer to Appendix document for report of survey results. The two major purposes of the Survey were to: a) determine the research experience of the Data Partners, and b) ascertain the Data Partners' interest in using the Mini-Sentinel Distributed Database for the conduct of clinical trials. CTTI conducted the survey from August 2-20, 2013. The survey was administered using Duke University's Qualtrics Survey Software and was distributed electronically to Mini-Sentinel principal investigators at the 18 Data Partners. CTTI and MSOC were blinded to the respondents' identities. CTTI compiled and analyzed the results which are presented in aggregate format in this report. Responses were received from 16 of the 18 Data Partners. The majority of respondents were the Mini-Sentinel principal investigators. Three respondents indicated that they received input from other individuals in filling out the survey. The 16 responding organizations consisted of 12 health delivery systems, three health insurance plans, and one academic institution.

B. RESULTS: OVERALL IMPRESSION

The Mini-Sentinel Data Partners have experience and expertise in a broad array of research activities. They are well-prepared to perform trials and, with few exceptions, organizational or infrastructure changes would not be needed. Their experience leads them to be selective in choosing to participate in specific studies, and the protocols most likely to be embraced are those that are crafted so they do not interfere with the plans' ongoing activities and needs. The organizations consider many factors when deciding whether they are willing to participate in a specific study. The complete Survey Report is provided in **Appendix A**. We describe the detailed results below.

1. Results: Previous experience

All respondents reported that their organization had participated in research studies, broadly defined. 15 had taken a full role in at least one study, defined as having collaborated in protocol development, identified and recruited research participants and healthcare providers, and provided follow-up data. 15 also reported that their organization had participated in a randomized trial in which individual patients were randomized, and 10 had participated in a trial in which clinicians or clinician organizations were randomized (two organizations did not know). The most common types of trials were of different educational messages (12), different diagnostic tests or procedures (12), and different therapies (12). Two had participated in trials assessing different economic incentives. 14 had identified eligible patients from claims, billing, or laboratory results data, 11 from electronic medical records, 11 from research coordinators or nurses, and 10 through a disease or case management system. Registries (6), surveys (6), and internet/social media (5) were used by some Data Partners. All 16 respondents indicated they have

contacted potential subjects by postal mail and telephone; eight had done so by email and seven by internet or social media.

All organizations had contacted patients directly regarding research studies for several reasons: to gauge interest (16), to collect information to confirm individual eligibility (15), to obtain informed consent (15), to collect patient-reported outcomes (15) and to debrief them (7). Outcome data had been collected or provided from claims data (15), electronic medical records (14), laboratory results (14), out-of-system medical records (13), radiology or imaging records (13), surveys and questionnaires (13), disease or case management systems (8), and registry data (7).

Respondents were asked whether their organization had experience in any of 17 specified research activities or roles, as well as whether the organization was able and had the resources in place to fill such roles in the future. The majority (typically 12 or more) reported having experience with most of these roles. Exceptions were experience identifying potential healthcare providers for which six had experience and eight had experience recruiting healthcare providers to manage research treatment/data collection.

2. Results: Willingness to participate in trials using the Mini-Sentinel infrastructure

Seven Data Partners (44%) indicated their organization is interested in participating in randomized clinical trial research and nine (56%) responded “Maybe.” In spite of this unanimous willingness to consider participating in trials, a surprising finding was that when asked about specific roles, respondents seemed less willing and able to engage in such trials. Although the majority (typically 12 or more) reported having experience with various roles, typically fewer than half said their organization would be willing and able to fill them again. One possible reason for this apparent paradox may be that respondents did not feel they could commit to being willing or able without more information and adequate funding for resources. Respondents frequently reported they were willing and able to perform roles ancillary to participant recruitment, including writing protocols and manuscripts, interpreting data, collecting baseline and outcome data through the Mini-Sentinel Distributed Dataset, evaluating feasibility of trials, and determining subject eligibility (seven for each of these). Six respondents were willing and able to collect documentation of treatment/intervention. Five respondents reported both experience and willingness to identify participants, manage informed consent processes, randomize patient/provider participants, and implement interventions (Table 2).

Table 2. Number of responders indicating their organization is able, with resources in place and, willing to participate in key research activities.

RESEARCH ACTIVITY	ABLE & WILLING	ABLE & NOT WILLING	WILLING BUT NOT ABLE	NOT ABLE & NOT WILLING	NO RESPONSE
Identifying participants using Mini-Sentinel	5	2	2	7	

RESEARCH ACTIVITY	ABLE & WILLING	ABLE & NOT WILLING	WILLING BUT NOT ABLE	NOT ABLE & NOT WILLING	NO RESPONSE
Distributed Dataset					
Managing informed consent process	5	1	2	8	
Randomizing recruited patients	5	0	3	7	1
Implementing intervention	5	0	3	7	1

Most respondents identified the following factors as important to a decision to participate in an IRB approved trial: staff capacity, funding reimbursement adequately covers work, organizational structures in place, type of work required, topic of the research, ethical concerns about project, risk of PHI disclosure, and risk of violating CMS rules about Medicare/Medicaid insurance delivery.

3. Results: Organizational and infrastructure needs

Most respondents indicated that organizational or infrastructure changes would not be needed to support adequately resourced randomized trial activities (**Table 3**). One respondent indicated that a change would be needed in order to work with healthcare providers.

Table 3. Number of respondents needing organizational or infrastructure changes per research activity

ARE ORGANIZATIONAL CHANGES NEEDED TO:	NO	YES/MAYBE	NO RESPONSE
Obtain IRB Approval for Studies?	13	3	
Identify Patients?	13	2	1
Contact Patients?	14	2	
Consent and Enroll Patients?	13	2	1
Collect Patient Data?	14	2	
Identify Healthcare Providers	12	4	
Recruit Healthcare Providers	12	4	
Work With Healthcare Providers to Implement Study?	10	6	
Manage Data and Data Collection?	13	3	
Collaborate in Clinical Trial Design and Analysis?	13	3	

4. Results: Identifying potential subjects

All respondents reported having existing mechanisms for obtaining laboratory data: 14 had existing mechanisms for claims or billing data and 12 kept electronic medical records. 10 reported that there was an existing mechanism for a research coordinator or nurse in a clinical department to identify eligible patients. Eight respondents indicated established mechanisms for using disease or case management system data, registry data, surveys and questionnaires, and internet or social media. Respondents most

commonly indicated that substantial barriers for identifying eligible patients exist with internet/social media.

5. Results: Identifying and engaging relevant clinicians

All organizations, except one, were able to identify clinicians who could potentially be involved in a trial, though four expressed hesitancy and indicated that extra approvals would be needed. Organizations who did not express definitive interest in participating in trials (i.e., responded “Maybe” on the global question described above) were more likely to report limitations.

For those who were able, most would work directly with the clinicians and three would refer clinicians to the researchers. Barriers to inviting clinicians to implement a research protocol included: funding reimbursement does not adequately cover the work (10), formulary implications (e.g., study involves non-formulary agents) (9), provider opting out of non-claim communication (3), provider contractual reasons (2), might not have the most recent provider information (2), provider does not have time (2), and organization prohibited from communicating with providers outside of claims processing (1). Organizations that expressed definitive interest in participating in trials were less likely to report barriers.

6. Results: Contacting potential subjects

All organizations, except one, are able to obtain patient contact information. Potential barriers include:

- HIPAA, IRB review,
- “we do not provide it to anyone outside of our plan”,
- “a few members are on ‘do not contact’ listing”,
- “organization does not contact dis-enrolled members”, and
- “contact information is not always accurate”.

All organizations can contact patients by mail or telephone, nine by email, eight by internet/social media, and four by other methods (in person or portal such as EpicCare’s myChart).

Organizations thought they could potentially do an array of activities when contacting potential subjects:

- tell them about the study to determine interest (15),
- collect more information to confirm eligibility (15), obtain informed consent (14),
- collect patient-reported outcomes (14), and
- tell them what study group they are assigned to (10).

7. Results: Using the Mini-Sentinel Distributed Database for exposures and outcomes

Data sufficient to identify many exposures and outcomes are currently contained in the Mini-Sentinel Common Data Model. Nine respondents indicated there would be constraints to using these data for research, six thought there would be no constraints and one did not know. IRB approval and consents were the most commonly-cited constraint, and one indicated business interests as a constraint.

Constraints were more commonly identified by respondents who said “Maybe” rather than “Yes” to the global question about their organization’s willingness to participate in randomized clinical trial research. Five Data Partners thought there would be no challenges to following patients and their exposures and outcomes over time, eleven identified problems when patients change health plans, and one reported that providers or plans do not permit use of diagnosis or procedure codes for research.

8. Results: Obtaining full-text medical records

Charts are currently obtained to validate exposures and outcomes in Mini-Sentinel protocols. 11 Data Partners said that their organization was as likely to obtain medical records from healthcare providers for research as for the public health protocols, and five said somewhat less likely. All respondents who said “yes” to the global question about their organization’s willingness to participate in randomized research agreed that accessing medical records for research would be as likely as for public health protocols.

C. COMMENTS ABOUT THE THREE USE CASES

Judged against the desirable characteristics laid out in this report for a clinical trial to be done within the Mini-Sentinel Distributed Database, the three use cases have several strengths. All three involve important practice questions that need to be answered and will likely match well with priorities of health delivery systems and/ or health insurance plans. Each involves interventions likely to be acceptable to members and providers because they compare established interventions. Proposed study populations are relatively broad and involve inclusion and exclusion criteria and clinical outcomes measurable with electronic data.

The use cases also serve to highlight how challenges will vary with study question and study design. For instance, engaging providers was one of the trial activities that seemed more challenging for Data Partners in the survey. Use case 2 (EDGE) is an example of a study that could be efficiently conducted by research staff rather than clinicians. Staff would implement the consent process and one-time drug withdrawal intervention after physician approval. Use case 3 (TERRIFIC) which relies on providers to prescribe the randomized therapy, would be expected to pose more challenges especially with the Data Partner organizations that do not provide direct patient care. Use case 1 (IMPACT-AF) which does not require provider agreement to invite patients to participate in the research will be less challenging than use case 2 (EDGE) which does. Use case 2 (EDGE) investigators will need to consider supplemental methods for collecting follow-up data due to disenrollment. Investigators for use cases 1 (IMPACT-AF) and 3 (TERRIFIC) will need to ensure that Data Partner organization and stakeholder concerns about cluster-randomized designs are assuaged. Cluster-randomization will be more difficult for national health insurance plans because healthcare providers see patients who have a variety of insurers. This problem could be mitigated by creating clusters that include only one participating Data Partner.

Common operational characteristics that will need to be addressed for all three use cases are:

- Obtaining the required approvals, so that the intervention meshes with Data Partner organization activities (e.g., guidelines, formularies).
- Satisfying local rules (i.e., health insurance plan or health delivery system) and obtaining needed agreements for centralized informed consent (or for achieving consensus on whether consent is needed).
- Developing and pre-testing procedures for patient and provider recruitment

D. CONCLUDING REMARKS

There appears to be considerable cause for optimism about the feasibility of using the Mini-Sentinel infrastructure to facilitate patient recruitment and follow-up of participants in randomized trials. The Mini-Sentinel Data Partner organizations have a high degree of experience with most aspects of individually randomized trials and there was a general overall willingness to consider participating in randomized trials using the Mini-Sentinel infrastructure. Their experience leads them to be selective in choosing to participate in specific studies, and the protocols most likely to be embraced are those that are crafted so they do not interfere with the plans' ongoing activities and needs. Respondents indicated a variety of factors that would be important to consider before deciding whether to participate in any given protocol. One area that seemed more challenging for some Data Partners was engaging clinicians, especially if a protocol required a more time-consuming role from them, such as performing randomization and implementing interventions.

VII. PRIVACY SUBGROUP REPORT: USES OF THE MINI-SENTINEL DISTRIBUTED DATABASE BEYOND SURVEILLANCE

This section explores major laws and regulations that affect whether, and under what conditions, the Mini-Sentinel Distributed Database can be utilized for purposes beyond post-market safety surveillance for drugs and devices. Uses of the Mini-Sentinel Distributed Database intended to contribute to “generalizable knowledge” will be considered to be research.ⁱⁱ Mini-Sentinel Data Partners who are “covered entities” under HIPAA (or are business associates of covered entities) will need to adhere to the provisions of the HIPAA Privacy Rule governing uses of protected health information for research purposes. To the extent a study submitted to the Mini-Sentinel Distributed Database is federally funded (or if there are Data Partners who have agreed to be bound by federal research rules for any research conducted using data under their stewardship), the federal human subjects protection law, called the Common Rule, may apply as well. Below, this paper sets forth how the use cases would be treated under HIPAA and the Common Rule. Consideration of circumstances in which regulations governing IND or Investigational Device Exemptions (IDE) impact the research activity is beyond the scope of this document.

A. USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE TO “PREPARE FOR RESEARCH”

To use individually identifiable health information (“Protected Health Information” or “PHI”) for activities to prepare for research, HIPAA includes special provisions that do not require patient authorization. However, the Common Rule treats the use of PHI to prepare for research as a research activity itself.

1. HIPAA requirements

Under the Privacy Rule, Data Partners may internally use PHI – or provide access to PHI to outside researchers – for activities to prepare for research, if the Data Partners receive a written statement from the researchers that:

1. The PHI is sought solely to prepare for research;
2. The PHI is necessary to prepare for research; and
3. No information identifying individuals will be removed from the premises in the course of the review.ⁱⁱⁱ

Preparation for research includes activities such as preparing a research protocol or developing a research hypothesis, identifying prospective research participants, or screening patient records to identify whether there are a sufficient number of patients at a facility or outpatient practice to function as a site for a clinical trial.^{iv} Each of the identified use cases above could require some research preparation activities on the part of the Data Partners. Actually contacting patients to solicit participation in a clinical trial is not an activity to “prepare for” research,^v and is covered in the next section.

2. Common Rule requirements

Even if the Privacy Rule does not require patient authorization or IRB waiver of authorization for “preparatory to research” activities, the Common Rule requires IRB waiver of informed consent. To the extent a Data Partner is subject to the Common Rule, a researcher would require waiver of informed consent to review identifiable patient information of living patients to identify potential research subjects.^{vi}

B. USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE FOR PATIENT RECRUITMENT PURPOSES

Each of the three use cases requires recruitment of patients to participate in the study. For patient recruitment (which, at least under HIPAA, is distinct from research preparation), HIPAA’s provisions permit Data Partners to contact their own members (or patients, if the Data Partner is a provider), and permit physicians and other healthcare providers to contact their patients, in order to recruit the individuals to participate in research, without requiring prior patient authorization to use PHI for these purposes. The Common Rule treats this activity the same way it treats any research uses of identifiable health data, requiring IRB waiver to use health information for recruitment.

1. HIPAA requirements

HIPAA permits the use or disclosure of PHI for patient recruitment.^{vii} Contact of patients for recruitment purposes by healthcare providers constitutes “treatment,” which is permitted by HIPAA without individual authorization.^{viii} This also would permit health insurance plans to disclose to a health provider a list of that provider’s patients for recruitment, because health insurance plans may disclose PHI to a provider for that provider’s treatment activities. Contact of health insurance plan members by a health plan for recruitment constitutes “health care operations” of the health insurance plan, which also is permitted by HIPAA without individual authorization.^{ix} HIPAA allows covered entities to share PHI for their respective “health care operations” purposes as long as the sharing entities have relationships with the individuals whose information is being shared.^x Either a healthcare provider or health insurance plan also may use a

non-employed third party (including the researcher) to contact patients for recruitment purposes, but would first have to obtain a business associate agreement with the third party.^{xi}

2. Common Rule requirements

Under the Common Rule, patient recruitment is “human subject research” that is governed by the federal regulations and requires IRB review.^{xii} Thus, even if the patient recruitment activities do not require IRB approval under the HIPAA Privacy Rule, access to information about potential human subjects and contacting those prospective subjects is “human subject research” that requires such review. The Common Rule allows IRBs to partially waive the requirement for authorization, so that authorization is not required for the initial contact, but will be sought for enrollment in the study.^{xiii}

C. USE OF THE MINI-SENTINEL DISTRIBUTED DATABASE TO CONDUCT RESEARCH

The use cases all involve randomization, either of patients or research sites, in order to answer a particular research question. The Mini-Sentinel Distributed Database Data Partners actually participating in the conduct of research will need to comply with HIPAA with respect to their internal uses of identifiable information for research purposes, and for any disclosures of information for research purposes. The Common Rule, when it applies, also sets forth rules regarding the treatment of human subjects of research, including uses of their identifiable information.

During the Mini-Sentinel pilot, Data Partners internally accessed PHI in order to apply specific safety surveillance questions coming from the FDA; results were provided to the Mini-Sentinel Coordinating Center, and then to the FDA, in either “de-identified” or “limited data set” form. For purposes of the analysis below, we presume that research uses of the Mini-Sentinel Distributed Database will follow the same process, with Data Partners internally conducting the research using identifiable information and disclosing only results in de-identified or limited data set form to the research sponsor.

1. HIPAA and Common Rule research requirements – Internal uses of Protected Health Information

Under the HIPAA Privacy Rule, Covered Entities may use PHI internally for research only if:

- The research participant or the participant’s authorized representative has signed a written HIPAA authorization;
- An IRB has waived the requirement for authorization; or
- The research involves only the information of decedents and required representations are obtained from the researchers.

a) Research uses with patient authorization

The most common way to meet the HIPAA requirements in a research protocol that involves a face-to-face interaction with an individual is to obtain a HIPAA-compliant authorization form.^{xiv} Depending on the particular use case and how it is implemented, collection of the HIPAA authorization form may be done by

the Data Partner, the patient’s healthcare provider, or both. A copy of the signed authorization must be given to the subject.

Previously, a HIPAA-compliant research authorization had to be limited to a particular research protocol or study.^{xv} However, these rules were changed effective March 23, 2013, and HIPAA authorization forms may now seek permission to use PHI more generally in “future research,” as long as an individual signing the authorization would know that his or her PHI would be used for future research. The Office for Civil Rights (“OCR”), the agency that enforces the HIPAA Rules, does not require any particular language to be used to describe the future research, which leaves substantial flexibility in implementation.^{xvi} The Common Rule also permits an informed consent document to seek consent to use a research participant’s information in future research as long as the future research is described in enough detail to allow the consent to be informed.^{xvii}

This suggests that an individual could be asked to provide authorization for future research uses upon enrollment or re-enrollment with a health insurance plan or during a visit with a healthcare provider, as long as the patient understood that she had the right to decline authorization to participate in the research and still enroll in the health insurance plan or be treated by the healthcare provider.^{xviii}

b) Waivers of authorization requirement

If it is not feasible to get research participants’ authorization, both HIPAA and the Common Rule allow researchers to ask an IRB to waive the requirement. Under HIPAA, to have the IRB grant this request, the researcher must demonstrate three things:

- The use or disclosure of the participants’ identifiable information involves no more than minimal risk to their privacy, based on: a) an adequate plan to protect information identifying the participants from improper use and disclosure; b) an adequate plan to destroy information identifying the participants at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retention or if retention is required by law); and c) adequate written assurances that the information identifying the participants will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research permitted by the rules;
- The research could not practicably be conducted without the waiver or alteration of authorization; and
- The research could not practicably be conducted without access to and use of information identifying the participants.^{xix}

If the researchers can get HIPAA authorization from the participants for some purposes but not others, the researchers can ask the IRB for partial waiver or alteration of the authorization. For example, researchers can ask the IRB to waive authorization for the initial review of records to determine which patients may be appropriate subjects, or may ask the IRB to approve verbal authorization if the contact with the subjects will be by phone.

The HIPAA Privacy Rule and Common Rule requirements are strikingly similar in this respect. In order for an IRB to waive informed consent under the Common Rule, the IRB must find that: (1) the research involves no more than minimal risk to the participants; (2) the waiver or alteration will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation.^{xx} With respect to the Mini-Sentinel Distributed Database use cases, the waiver must be obtained by (or on behalf of) the entity seeking to access, use or disclose PHI for research purposes. As with obtaining authorization, this may be an obligation of the Data Partners, the providers, or both, depending on the use case and how it is implemented.

2. HIPAA and Common Rule requirements re: disclosures of research results

If research using the Mini-Sentinel Distributed Database uses the process utilized in the Mini-Sentinel Pilot for the conduct of safety surveillance, information disclosed by Data Partners conducting research will qualify as either de-identified data or a limited data set under HIPAA. Such data is treated with much less regulatory scrutiny under both HIPAA and the Common Rule.

a) De-identified data under HIPAA

Data that meets the definition of “de-identified” under HIPAA is not subject to the Privacy Rule and can be disclosed for research purposes without constraints. HIPAA permits two ways to “de-identify” information before a researcher (or someone on behalf of a researcher) reviews, collects or releases information for research:^{xxi}

- i. Safe Harbor: Remove or code 18 “identifiers” from the information.^{xxii} If the covered entity has actual knowledge that, even with these identifiers removed, the remaining information could be used alone or in combination with other information to identify the individual, then the information still must be treated as PHI. If the identifiers are coded before being released for research, the code may not be derived from any information about the patient or plan member.
- ii. Statistical or Statistician Method: Have a qualified statistical expert determine that the risk is very small that the identifiers present could be used alone, or in combination with other available information, to identify the patient. The statistical expert must be a person with knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information non-individually identifiable, and must document the methods and results of the analysis that justifies the conclusion of very small risk. The HIPAA covered entity must keep this documentation for six years.

b) Common Rule and “de-identification”

The treatment of de-identified information under the Common Rule is somewhat different. An entity does not conduct “human subject research” under the HHS regulations if the specimens were not collected for currently proposed research and the investigator cannot readily ascertain the identity of the subjects.^{xxiii}

To de-identify information under the Common Rule, therefore, only removal of direct identifiers (those identifiers that enable an investigator to readily ascertain the identity of a subject) is necessary.^{xxiv}

c) Disclosure of a Limited Data Set

i. HIPAA

A “Limited Data Set” is partially de-identified patient information. A Limited Data Set excludes all of the “identifiers” required to be removed under the Safe Harbor method (see endnote), except that a Limited Data Set may include: (1) geographic designations above the street level or PO Box; (2) dates directly related to a patient, such as dates of service, birth date, admission date, discharge date, or date of death; or (3) any other unique identifying number, characteristic, or code that is not expressly listed as an “identifier.”^{xxv} The recipient of a Limited Data Set must sign a “Data Use Agreement” in which they agree to protect the confidentiality of the information.^{xxvi}

ii. Common Rule

Because a Limited Data Set does not contain any direct identifiers, a Limited Data Set most likely will be treated as non-identifiable information under the Common Rule, if the investigator cannot readily ascertain the identity of the subjects.

D. NEW HIPAA RULES REQUIRING PRIOR PATIENT AUTHORIZATION FOR “SALE” OF PHI ARE NOT APPLICABLE

Section 13405(d) of the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH) (*codified at* 42 U.S.C. § 17935(d)) required changes in the HIPAA regulations to prohibit a covered entity or business associate from receiving remuneration, either direct or indirect, in exchange for the PHI, unless the covered entity obtains the authorization of the subject(s) of the information.^{xxvii}

HITECH, and the implementing regulations (now part of HIPAA) incorporate a number of exceptions where authorization is not required, including an exception for research where “the only remuneration received by the covered entity or business associate is a reasonable cost-based fee to cover the cost to prepare and transmit the protected health information for such purposes.”^{xxviii} The OCR has opined that payment for research services – even if those services involve the provision of PHI – will not be treated as a “sale of PHI.” Instead, the prohibition applies where a covered entity or business associate *primarily* is being compensated to supply PHI.^{xxix} In the case of the Mini-Sentinel Distributed Database, if remuneration is provided to Data Partners to support the performance of research, that remuneration is provide for services provided by the Data Partners, including formatting data in the Common Data Model, running queries on that data, and providing responses to those queries. These are research services, and any data disclosed is part of the research. Consequently, remuneration to the Mini-Sentinel Distributed Database Data Partners does not constitute a “sale” of PHI under HIPAA as amended by HITECH.

E. ADDITIONAL USES OF THE MSDD AUTHORIZED BY FDA

The Food and Drug Administration Amendments Act of 2007 (FDAAA)^{xxx} also provides a source of authority for use of the MSDD for purposes beyond postmarket safety surveillance. In FDAAA, Congress authorized FDA to develop a large-scale data infrastructure in the form of a 100-million-person postmarketing “risk identification and analysis system”^{xxxi} that relies on administrative data (such as health insurance claims information) and clinical records.^{xxxii} This system is also called the Sentinel System^{xxxiii} and its pilot phase, Mini-Sentinel, already is operating.^{xxxiv} This discussion uses “Sentinel” to refer generally to this infrastructure, unless the context calls for a distinction between Sentinel and Mini-Sentinel.

FDAAA added two sections to the Food, Drug, and Cosmetic Act that define purposes for which Congress authorized Sentinel to be used:

- 21 United States Code (“U.S.C.”) Section 355(k)(3) authorizes FDA to develop the Sentinel infrastructure and also authorizes basic uses of Sentinel to support FDA’s own regulatory oversight of drug safety during the postmarketing period after drugs are approved.
- 21 U.S.C. Section 355(k)(4) is entitled “Advanced Analysis of Drug Safety Data” and authorizes additional uses of Sentinel. These include uses of Sentinel by “qualified” outside entities^{xxxv} that can include private-sector commercial and academic organizations, as well as other governmental agencies. Section 355(k)(4) lists additional uses of Sentinel that Congress has specifically authorized. It then sets out procedures and safeguards FDA must follow to allow such uses.

To date, FDA has used Mini-Sentinel exclusively to support the agency’s own postmarketing oversight of medical product safety.^{xxxvi} These uses, which correspond to activities authorized in Section 355(k)(3), clearly constitute public health uses of Sentinel.^{xxxvii} In Section 355(k)(4), Congress authorized FDA to allow access to Sentinel for a defined set of additional uses, subject to strict statutory provisions to protect patient privacy and to ensure appropriate FDA oversight of the additional uses of Sentinel.

FDAAA provides a statutory basis to use Sentinel for studies unrelated to FDA’s own regulatory oversight of clinical drug safety. FDAAA Section 355(k)(4) authorizes FDA to establish collaborations with public, academic, and private entities for advanced analysis of the “drug safety data described in paragraph (k)(3)” – in other words, the data in the Sentinel system.^{xxxviii} FDA already has been entering Section 355(k)(4) collaborative agreements with the Mini-Sentinel Data Partners, the data-holding institutions that voluntarily supply data for inclusion in Mini-Sentinel.^{xxxix} However, Section 355(k)(4) does not limit FDA to collaborations with data *suppliers* and also allows FDA to collaborate with data *users*.^{xl} Congress envisioned that FDA “may routinely contract”^{xli} with outside collaborators to perform studies that use Sentinel data. This use of the word “routinely” indicates congressional intent for these collaborations to be an ongoing part of Sentinel’s operations – not just as a way to procure data during the Sentinel start-up but as an ongoing way to arrange and fund ongoing studies that use Sentinel.

As an abbreviation, this section adopts the phrase “collaborative data use agreements” (CDUAs) to refer to contracts FDA can enter under 21 U.S.C. § 355(k)(4) with outside entities that wish to conduct studies that use the data resources of Sentinel. CDUAs under Section 355(k)(4) are the major statutory mechanism Congress created to allow additional uses of Sentinel.^{xiii} Pursuant to a CDUA, entities other than FDA would be able to submit queries to Sentinel. The negotiated terms of the CDUA could require the outside user to fund costs that the Data Partners and Mini-Sentinel Operation Center will incur in responding to the user’s queries.^{xliii}

Based on the statutory language, FDAAA allows Sentinel be used for certain studies of effectiveness and comparative effectiveness, in situations where a drug’s failure to produce its expected treatment response exposes patients to certain “serious” events that FDAAA defines. While FDAAA would allow a fairly broad range of studies to proceed under CDUAs, there will be some studies that would not qualify.

1. Scope of authority for additional uses of Sentinel

Congress did place some constraints on the FDA’s authority to enter CDUAs. Access to Mini-Sentinel under a CDUA is only available for studies that serve one of the five listed purposes in subsections (I) - (V) of the statute below:

§ 355(k)(4)(D) Procedures for the development of drug safety collaborations

(i) In general

Not later than 180 days after the date of the establishment of the active postmarket risk identification and analysis system under this subsection, the Secretary shall establish and implement procedures under which the Secretary may routinely contract with one or more qualified entities to--

- (I) classify, analyze, or aggregate data described in paragraph (3)(C) [Sentinel] and information that is publicly available or is provided by the Secretary;
- (II) allow for prompt investigation of priority drug safety questions, including--
 - (aa) unresolved safety questions for drugs or classes of drugs; and
 - (bb) for a newly-approved drugs, safety signals from clinical trials used to approve the drug and other preapproval trials; rare, serious drug side effects; and the safety of use in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children);
- (III) perform advanced research and analysis on identified drug safety risks;
- (IV) focus post-approval studies and clinical trials under subsection (o)(3) of this section more effectively on cases for which reports under paragraph (1) and other safety

signal detection is not sufficient to resolve whether there is an elevated risk of a serious adverse event associated with the use of a drug; and

- (V) carry out other activities as the Secretary deems necessary to carry out the purposes of this paragraph.

The first four allowed purposes (see items (I) - (IV) above) are stated in expansive language. For example, item (II)(aa) allows Sentinel to be used to study “unresolved safety questions.” The fifth purpose (see item (V)) is a broad grant of discretion for the Secretary of HHS to authorize access to Sentinel for virtually any purpose she deems necessary to fulfill the first four broadly stated purposes. Congress delegated to the agency the task of interpreting these provisions and making day-to-day decisions about which uses of Sentinel fit within the five congressionally authorized purposes.

To appreciate the breadth of FDA’s statutory authority to allow additional uses of Sentinel, however, it is crucial to understand how FDAAA defines safety. FDAAA defines safety in a way that encompasses certain questions about the effectiveness of approved drugs. As a result, the agency’s power to approve additional uses of Sentinel under subsections 355(k)(4)(D)(i)(I) - (V) is broader than a mere power to allow studies of drug toxicity and other traditional “safety” problems. It includes the power to authorize access to Mini-Sentinel for various types of studies related to the effectiveness of approved drugs.

2. Statutory authority under FDAAA to use Sentinel to examine questions related to drug effectiveness

Section 355(k)(4) specifically authorizes FDA to enter collaborations with outside entities to “improve the quality and efficiency of postmarket drug safety risk-benefit analysis.”^{xliiv} The reference to benefits as well as risks displays clear congressional intent for Mini-Sentinel to be used to explore effectiveness questions that bear on a drug’s risk/benefit ratio. Additional statutory support is found in the list of qualified entities with which FDA can enter CDUAs.^{xliv} The list includes entities that have “[e]xperience with, and expertise on, the development of drug safety and effectiveness research using electronic population data”^{xlvi} and entities with an “understanding of drug development or risk/benefit balancing in a clinical setting.”^{xlvii}

However, the crucial question to be posed is: *Which* types of effectiveness studies are allowed under a CDUA? As discussed earlier, Congress authorized FDA to use Sentinel for the basic regulatory purposes listed in subsections 355(k)(3)(C)(1)(I)-(V) and to enter CDUAs for collaborative studies that serve the additional purposes listed in subsections 355(k)(4)(D)(i)(I) - (V). These purposes must be construed in light of FDAAA’s definitions of key terms like “adverse drug experience” and “serious risk” and “safety.”

Section 355(k)(3), which authorizes creation of Sentinel, adopts^{xlviii} the definitions of these terms that appear in the REMS provisions of FDAAA.^{xlix} The term “adverse drug experience”¹ is defined as meaning:

“any adverse event associated with the use of a drug in humans, whether or not considered drug related, including --

- A. an adverse event occurring in the course of the use of the drug in professional practice;
- B. an adverse event occurring from an overdose of the drug, whether accidental or intentional;
- C. an adverse event occurring from abuse of the drug;
- D. an adverse event occurring from withdrawal of the drug; and
- E. any failure of expected pharmacological action of the drug.”ⁱⁱ

Note that subsection (E) of this definition treats failures in a drug’s expected effectiveness as adverse drug experiences. This places a broad range of questions about the effectiveness of approved drugs on a par with questions about toxicity and abuse potential and other things traditionally regarded as safety issues. FDAAA then defines a “serious” adverse drug experience as one that kills or places the patient at immediate risk of death, results in persistent or significant incapacity or substantial disruption of ability to conduct normal life functions, or which may require medical or surgical intervention to prevent such outcomes.ⁱⁱⁱ Finally, FDAAA equates “serious risk” to risk of a serious adverse drug experience.ⁱⁱⁱⁱ

Together, these definitions mean that FDA has a statutory basis to enter CDUAs that would allow access to Sentinel for studying *some* questions about the effectiveness of approved drugs. To qualify, the concerns about a drug’s effectiveness have to be “serious” in the sense that an ineffective treatment has the potential to:

(A) result in

- (i) death;
- (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);
- (iii) in-patient hospitalization or prolongation of existing hospitalization;
- (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- (v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).^{liv}

Effectiveness questions pose “serious” risks if they have the potential to create the sorts of problems just described. Congress has authorized FDA to enter CDUAs that allow Mini-Sentinel to be used to conduct effectiveness studies that are “serious” in this sense.

Studies of drug effectiveness that do not meet this threshold would be ineligible for CDUAs. However, many studies of effectiveness would be eligible. For example, an effectiveness issue is “serious” under Section 355-1(b)(4)(A)(iv) if the drug’s failure to produce its expected treatment effect could cause “substantial disruption of the ability to conduct normal life functions.” This provision gives the agency rather broad discretion to determine that concerns about a drug’s effectiveness pose a “serious” risk as FDAAA defines this term.^{lv}

3. The mechanics of allowing access to Mini-Sentinel for uses authorized in Section 355(k)(4)

It is FDA’s responsibility to determine whether a particular study proposal meets FDAAA’s criteria for CDUAs. To meet these criteria, a study seemingly needs to examine safety and clinical outcomes *for FDA-approved drugs*. Studies of other treatment modalities do not appear to fit within Section 355(k)(4). Patient-level and cluster-level studies that examine the clinical safety and effectiveness of drugs or groups of drugs potentially could qualify as studies of “serious” risks, if the drugs are used to treat medical conditions (such as diabetes or heart disease) where a lack of effectiveness could lead to injurious deterioration in the patient’s overall condition.

4. Privacy compliance for access pursuant to CDUAs

Before entering a CDUA, Section 355(k)(4) requires FDA to determine that the outside data user is a qualified entity and FDA must formalize the CDUA via contract. Access to any health information pursuant to a CDUA would be a public health disclosure under the HIPAA^{lvi} Privacy Rule.^{lvii} Under the Privacy Rule, an entity that signs a contract with FDA gains the status of a “public health official”^{lviii} for purposes of the activities covered by that contract. When FDA enters a Section 355(k)(4) CDUA with a data user, the data user acquires the status of a public health official for purposes of the study covered by the CDUA. HIPAA-covered health insurance plans and health delivery systems who are Mini-Sentinel Data Partners thus would be able to make their data available for use in that study under HIPAA’s public health exception.^{lix} As discussed in an earlier Mini-Sentinel white paper, HIPAA’s public health exception does not require Data Partners’ IRBs to analyze whether a particular data use is “public health activity” or “research” and only requires the Data Partner to verify that the person seeking data access meets HIPAA’s verification standards.^{lix} This view of HIPAA’s public health exception is now accepted in the legal scholarly literature as well.^{lxi}

FDA’s CDUAs must, by statute, incorporate a number of privacy protections.^{lxii} First, section 355(k)(4)(B)^{lxiii} forbids the disclosure of any identifiable information when reporting the results of studies that use Sentinel under a CDUA. Outside entities whose queries are run under CDUAs can receive only de-identified summary results and would not have any direct access to any raw, identifiable data held by Mini-Sentinel or its Data Partners. Any party that enters a CDUA with FDA must agree to follow the HIPAA Privacy Rule.^{lxiv} Even if the outside entity is not a HIPAA-covered entity, it must agree to be bound contractually by the provisions of the HIPAA Privacy Rule.^{lxv} In addition, it must agree not to disclose any individually identifiable health information that it may receive while working under the CDUA.^{lxvi} It must establish appropriate security measures to protect the confidentiality and

privacy of all Sentinel data to which it has access^{lxvii} and may not share the data with its own corporate affiliates.^{lxviii} These obligations continue even after the CDUA ends.^{lxix}

Beyond these statutorily required protections, the FDA would be able to require additional privacy and data security requirements as part of the terms and conditions of its CDUAs.^{lxx} Thus, FDA can require data users to comply with all of the principles, policies, and technical specifications Mini-Sentinel has implemented to ensure conformity with fair information practices, to protect the privacy of individual health information, and to maintain strict data security.^{lxxi}

Mini-Sentinel relies on voluntary arrangements^{lxxii} with the Data Partners that supply data to the system. The FDA's CDUAs with third parties should contain terms satisfactory not only to the FDA, but also to the Data Partners. The business terms of these agreements would be a matter for the FDA, its data users, and the collaborative data users to negotiate. All such agreements, however, must incorporate the statutory privacy and data security protections just described, as well as any other privacy protections that FDA may choose to require.

F. CONCLUSION OF DATA PRIVACY CONSIDERATIONS

HIPAA permits Data Partners to access PHI in their records, and to contact healthcare providers caring for their members, in order to gather information in preparation for research and to recruit patients for participation in clinical trials, without need to first obtain authorization from those patients. HIPAA also permits Data Partners to access PHI for research purposes; however, prior patient authorization is required unless it is waived by an IRB. Disclosing de-identified data or a limited data set for research purposes does not require patient authorization.

Data Partners covered by the Common Rule will need informed consent prior to using identifiable information from patients for either: research preparation, recruitment or the conduct of research, unless such consent is waived by an IRB. The Common Rule does not apply to data that is not identifiable to a researcher.

FDA has the authority to determine if any of the proposed use cases for the MSDD can be conducted under CDUAs pursuant to FDAAA. Studies conducted under CDUAs will be treated as public health uses of the MSDD and the provisions governing research in HIPAA and the Common Rule will not apply.

VIII. OVERALL SUMMARY WITH RECOMMENDATIONS

There are substantial opportunities to improve the efficiency of clinical trial recruitment and implementation through partnerships with Mini-Sentinel Data Partners. Such trials will require alignment with the interests of the health insurance plans and their providers and the health delivery systems, and will involve planning activities that are not part of the development of traditional clinical trials. However, these additional steps may allow other activities to be performed more quickly and at lower total cost than conventional methods for identifying, enrolling, and following clinical trial participants. Neither the

Common Rule nor HIPAA provisions prevent implementation of such trials. Under some interpretations of FDAAA, it may be possible for FDA to enter into partnerships, with private sponsors that might enable some aspects of using the data for such trials, especially regarding the use of information developed as part of the Mini-Sentinel Distributed Database.

A potential next step could be to assess the potential eligible population for the three use cases, or for other potential trials of interest.

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X. ENDNOTES

- i Based on conversations with the FDA, it has been determined that the FDA’s regulations for the protection of human subjects (21 CFR Parts 50 and 56) will not apply to the use cases being proposed for additional uses of the Mini-Sentinel Distributed Database, as the use cases are not being conducted to facilitate submission of an application for regulatory approval or as a mandated post-market study.
- ii Under the Common Rule, research is defined as a “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” 45 C.F.R. §46.102(d). The HIPAA Privacy Rule similarly defines research as “systematic investigation[s]...[that] contribute to generalizable knowledge.” 45 C.F.R. § 164.501.
- iii If researchers will need to remove the information from the covered entity’s premises to review it, the researchers must ask the IRB to waive the required authorization, or another HIPAA option must be satisfied. OCR has provided the following guidance on when remote access to a server containing PHI is removing the PHI from the premises:

Remote access connectivity (i.e., out-of-office computer access achieved through secure connections with access permission and authentication) involves a transmission of electronic PHI, which is not necessarily a removal of PHI under the Privacy Rule. However, although the access to PHI through a remote access connection is not itself a removal of PHI, the printing, copying, saving, or electronically faxing of such PHI would be considered to be a removal of PHI from a covered entity.

The Privacy Rule permits a covered entity to rely on representations from persons requesting PHI if such reliance is reasonable under the circumstances. In the case of a request by a researcher to access PHI remotely, this means that, among other things, the risk of removal, as described above, should be assessed in order to determine whether it is reasonable to rely on the researcher’s representation that the PHI will not be removed from the covered entity. The covered entity should determine whether its reliance is reasonable based on the circumstances of the particular case.

For example, a covered entity may conclude that it can reasonably rely on representations from researchers who are its employees or contractors because their activity is manageable through the covered entity’s employment and related policies establishing sanctions for the misuse of PHI. On the other hand, where the researcher has no connection to the covered entity, the covered entity may conclude that it cannot reasonably rely on the researcher’s representations that PHI will not be removed from the covered entity, unless the researcher’s activity is managed in some other way.

Covered entities that permit their workforce or other researchers to access PHI via a remote access connection must also comply with ... the Security Rule’s requirements for appropriate safeguards to protect the organization’s electronic PHI. Specifically, the standards for access control (45 CFR § 164.312(a)), integrity (45 CFR § 164.312(c)(1)), and transmission security (45 CFR § 164.312(e)(1)) require covered entities to implement policies and procedures to protect the integrity of, and guard against the unauthorized access to, electronic PHI. The standard for transmission security (§ 164.312(e)) also includes addressable specifications for integrity controls and encryption. This means that the covered entity must assess its use of open networks, identify the available and appropriate

means to protect electronic PHI as it is transmitted, select a solution, and document the decision.
<http://privacyruleandresearch.nih.gov/pdf/HealthServicesResearchHIPAAPrivacyRule.pdf>.

- iv See Clinical Research and the HIPAA Privacy Rule (NIH), at p, 11, available at
http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf (hereinafter, “NIH Guidance”).
- v *Id.*
- vi See 45 C.F.R. § 46.102(d), (f) (defining “research on human subjects” as including examination of private information); 45 C.F.R. § 46.109(a) (requiring IRB approval of research on human subjects); 45 C.F.R. § 46.116(c) (IRB approval of consent procedure to waive informed consent).
- vii NIH Guidance, *supra* note 4, p. 4 (NIH 6/22/04), at 11.
- viii 45 C.F.R. § 164.501 and § 164.506.
- ix 45 C.F.R. § 501(c)(6); see also NIH Guidance, *supra* note 48, (“If the researchers is a workforce member of a covered entity, the researcher may contact the potential study participant, as part of the covered entity’s health care operations, for the purposes of seeking Authorization.”).
- x 45 C.F.R. § 164.506(c).
- xi 45 C.F.R. § 164.502(e) and § 164.504(e).
- xii See 45 C.F.R. § 46.102 (defining research and human subjects).
- xiii See NIH Guidance, *supra* note 4, p. 4 (Under the “preparatory to research” provision, covered entities may use or disclose PHI to researchers to aid in study recruitment. The covered entity may allow a researcher, either within or outside the covered entity, to identify, but not contact, potential study participants under the “preparatory to research” provision.)
- xiv The HIPAA authorization form must include a number of items:
- A specific and meaningful description of the PHI to be used or disclosed in the research (such as the subject’s medical records or other more limited portions of the record, such as laboratory results);
 - The name or specific identification of the persons or class of persons authorized to make the disclosure (such as the subject’s physicians and treating hospitals);
 - The name or specific identification of the persons or class of persons who will have access to the PHI (such as the research site, principal investigator, IRB, sponsor, other third parties involved in the research, data safety monitoring board, FDA, and HHS);
 - An expiration date or event (such as the end of the study), or a statement that the authorization has no expiration;
 - A statement of the subject’s right to revoke the authorization in writing and a description of how to do so;
 - A statement that the subject may not revoke the authorization as to information already disclosed for the research where the information is necessary to maintain the integrity of the study data, or a description of other exceptions where the subject may not revoke the authorization;
 - A statement that the entity disclosing the PHI may not condition treatment, payment, enrollment or eligibility for benefits on the subject signing the authorization. If the individual will not be allowed to participate in the clinical trial without signing the authorization, the authorization must include a statement to that effect;
 - A statement that the information disclosed for the research may be subject to redisclosure by the recipient and no longer be protected by the federal privacy rule;^{xiv}

- If the subject will not be given access to medical records during the study, a statement that the subject agrees to the denial of access when consenting to participate in the study, and that the right of access to the records will be reinstated upon completion of the study
- The subject’s signature and the date of signature; and
- If the authorization is executed by a personal representative of the subject (the subject’s health care decision maker), a description of that person’s authority to act for the subject. 45 C.F.R. § 164.508.

^{xv} 45 C.F.R. § 164.508. *See also* 67 Fed. Reg. at 53226 (Aug. 14, 2002).

^{xvi} *See* 78 Fed. Reg. 5612, 5613 (Jan. 15, 2013) (“[T]he Department no longer interprets the “purpose” provision at § 164.508(c)(1)(iv) as requiring that an authorization for the use or disclosure of protected health information for research purposes be study specific. In order to satisfy the requirement that an authorization include a description of each purpose of the requested use or disclosure, an authorization for uses and disclosures of protected health information for future”). *See also* 78 Fed. Reg. 5613 (Jan. 25, 2013) (“Covered entities and researchers have flexibility to describe the information to be used or disclosed for the future research, so long as it is reasonable from such description to believe that the individual would expect the information to be used or disclosed for the future research. We also clarify that a description of the protected health information to be used for the future research may include information collected beyond the time of the original study. Further, the Privacy Rule authorization requirements allow a “class of persons” to be described for purposes of identifying in the authorization the recipients of the protected health information. Thus, covered entities and researchers have flexibility in the manner in which they describe the recipients of the protected health information for the future research, so long as it is reasonable from such description to believe that the individual would expect his or her protected health information to be shared with such persons for the future research.”).

^{xvii} *See* 21 C.F.R. § 50.25; 45 C.F.R. § 46.116. *See also* *Institutional Review Boards and the HIPAA Privacy Rule* (HHS Aug. 15, 2003) at 11-12, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf.

^{xviii} New provisions in the HIPAA Privacy Rule now allow authorizations that patients are required to sign (e.g., in order to be treated or to enroll in a health plan) to be combined with authorizations that are at the patient’s option, as long as it is clear to the patient in the authorization that she has the right to decline participation in the optional activity. 78 Fed Reg. 5610 (January 26, 2013).

^{xix} 45 C.F.R. 164.512(i)(2)(ii).

^{xx} 45 C.F.R. § 46.117(c)-(d); 45 C.F.R. § 46.101(i) and 61 Federal Register 51531 (Oct. 2, 1996) (waiver of informed consent in emergency research).

^{xxi} 45 C.F.R. § 164.514(a)-(b).

^{xxii} List of identifiers that must be removed in order to meet the safe harbor method of HIPAA de-identification:

- Name
- Street address, city, county, precinct, or zip code (unless only the first three digits of the zip code are used and the area has more than 20,000 residents);
- The month and day of dates directly related to an individual, such as birth date, admission date, discharge date, dates of service, or date of death;
- Age if over 89 (unless aggregated into a single category of age 90 and older);
- Telephone numbers;

- Fax numbers;
- Email addresses;
- Social security numbers;
- Medical record numbers;
- Health plan beneficiary numbers;
- Account numbers;
- Certificate/license numbers;
- Vehicle identifiers, serial numbers, and license plate numbers;
- Device identifiers and serial numbers;
- Web Universal Resource Locators (URLs) and Internet Protocol (IP) addresses;
- Biometric identifiers, such as fingerprints
- Full-face photographs and any comparable images; or
- Any other unique identifying number, characteristic, or code.

^{xxiii} 45 C.F.R. § 46.102. *See also* See OHRP, “Guidance on Research Involving Coded Private Information or Biological Specimens” (Aug. 2004) at <http://hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>.

^{xxiv} Note that coding under the Common Rule follows different rules. The Office for Human Research Protections (“OHRP”) recently clarified that, in order to ensure that an investigator cannot determine the identity of the subjects in coded information: (1) the key to decipher the code must be destroyed before the research begins; (2) the investigator and the holder of the key must enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the subjects are deceased; (3) an IRB must approve written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or (4) other legal requirements prohibit the release of the key to the investigators, until the subjects are deceased. *Id.*

^{xxv} 45 C.F.R. § 164.514(c).

^{xxvi} A Data Use Agreement must include the following:

- (A) Establish the permitted uses and disclosures of such information by the limited data set recipient [the purpose of which must be limited to research, public health activities or health care operations]. The data use agreement may not authorize the limited data set recipient to use or further disclose the information in a manner that would violate the requirements of this subpart, if done by the covered entity;
- (B) Establish who is permitted to use or receive the limited data set; and
- (C) Provide that the limited data set recipient will:
- (1) Not use or further disclose the information other than as permitted by the data use agreement or as otherwise required by law;
 - (2) Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the data use agreement;
 - (3) Report to the covered entity any use or disclosure of the information not provided for by its data use agreement of which it becomes aware;
 - (4) Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the limited data set recipient with respect to such information; and

(5) Not identify the information or contact the individuals. 45 C.F.R. § 164.514(e)(4).

^{xxvii} See 45 C.F.R. § 164.502(a)(5)(ii):

Sale of protected health information:

(A) Except pursuant to and in compliance with § 164.508(a)(4), a covered entity or business associate may not sell protected health information.

(B) For purposes of this paragraph, sale of protected health information means:

(1) Except as provided in paragraph (a)(5)(ii)(B)(2) of this section, a disclosure of protected health information by a covered entity or business associate, if applicable, where the covered entity or business associate directly or indirectly receives remuneration from or on behalf of the recipient of the protected health information in exchange for the protected health information.

(2) Sale of protected health information does not include a disclosure of protected health information:

(i) For public health purposes pursuant to § 164.512(b) or § 164.514(e);

(ii) For research purposes pursuant to § 164.512(i) or § 164.514(e), where the only remuneration received by the covered entity or business associate is a reasonable cost-based fee to cover the cost to prepare and transmit the protected health information for such purposes;

(iii) For treatment and payment purposes pursuant to § 164.506(a);

(iv) For the sale, transfer, merger, or consolidation of all or part of the covered entity and for related due diligence as described in paragraph (6)(iv) of the definition of health care operations and pursuant to § 164.506(a);

(v) To or by a business associate for activities that the business associate undertakes on behalf of a covered entity, or on behalf of a business associate in the case of a subcontractor, pursuant to §§ 164.502(e) and 164.504(e), and the only remuneration provided is by the covered entity to the business associate, or by the business associate to the subcontractor, if applicable, for the performance of such activities;

(vi) To an individual, when requested under § 164.524 or § 164.528;

(vii) Required by law as permitted under § 164.512(a); and

(viii) For any other purpose permitted by and in accordance with the applicable requirements of this subpart, where the only remuneration received by the covered entity or business associate is a reasonable, cost-based fee to cover the cost to prepare and transmit the protected health information for such purpose or a fee otherwise expressly permitted by other law.

The authorization also must state that the disclosure will result in remuneration to the covered entity. 45 C.F.R. 164.508.

^{xxviii} 45 C.F.R. § 164.502(a)(5)(ii).

^{xxix} [W]e do not consider sale of protected health information in this provision to encompass payments a covered entity may receive in the form of grants, or contracts or other arrangements to perform programs or activities, such as a research study, because any provision of protected health information to the payer is a byproduct of the service being provided. Thus, the payment by a research sponsor to a covered entity to conduct a research study is not considered a sale of protected health information even if research results that may include protected health information are disclosed to the sponsor in the course of the study. Further, the receipt of a grant or funding from a government agency to conduct a program is not a sale of protected health information, even if, as a condition of receiving the funding, the covered entity is required to report protected health information to the agency for program oversight or other purposes. (Certain of these disclosures would also be exempt

from the sale requirements, depending on whether the requirement to report data was included in regulation or other law.)... In contrast, a sale of protected health information occurs when the covered entity primarily is being compensated to supply data it maintains in its role as a covered entity (or business associate). ... For example, a disclosure of protected health information by a covered entity to a third party researcher that is conducting the research in exchange for remuneration would fall within these provisions, unless the only remuneration received is a reasonable, cost-based fee to cover the cost to prepare and transmit the data for such purposes (see below). *See Id.* at 5607, 5608.

xxx Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

xxxi 21 U.S.C. § 355(k)(3).

xxxii *See* Richard Platt et al., *The U.S. Food and Drug Administration’s Mini-Sentinel Program: Status and Direction*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1, 3 (2012) (discussing Mini-Sentinel’s distributed architecture); *see also* Lesley Curtis et al., *Design Considerations, Architecture, and Use of the Mini-Sentinel Distributed Data System*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 23, 28 (2012) (discussing the types of data included in the system); Melissa Robb et al., *The U.S. Food and Drug Administration’s Sentinel Initiative: Expanding the Horizons of Medical Product Safety*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 9, 9-10 (discussing applications of the system).

xxxiii Rachel E. Behrman et al., *Developing the Sentinel System—A National Resource for Evidence Development*, 364 NEW ENG. J. MED. 498, 498 (2011); *see also* OFFICE OF CRITICAL PATH PROGRAMS, DEP’T OF HEALTH & HUMAN SERVS., *THE SENTINEL INITIATIVE* (2008), *available at* <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf>; *FDA’s Sentinel Initiative*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm> (last updated Aug. 16, 2012).

xxxiv Curtis et al., *supra* note 32, at 28.

xxxv 21 U.S.C. § 355(k)(4)(A)(ii), 355(k)(4)(F).

xxxvi *See* Letter from Rachel Behrman, Sentinel Initiative, Exec. Sponsor, to Richard Platt, Professor & Chair of Dep’t of Ambulatory Care & Prevention, Harvard Med. Sch. & Harvard Pilgrim Health Care (July 19, 2010), *reprinted in* KRISTEN ROSATI, BARBARA EVANS & DEVEN MCGRAW, *HIPAA AND COMMON RULE COMPLIANCE IN THE MINI-SENTINEL PILOT* 1, 12-14 (2010), *available at* http://mini-sentinel.org/work_products/About_Us/HIPAA_and_CommonRuleCompliance_in_the_Mini-SentinelPilot.pdf; *see also* Platt et al., *supra* note 32, at 6.

xxxvii *Id.*

xxxviii *Id.* § 355(k)(4)(A).

xxxix Platt et al., *supra* note 32, at 1.

xl *See* Barbara J. Evans, *Authority of the Food and Drug Administration to Require Data Access and Control Use Rights in the Sentinel Data Network*, 65 FOOD & DRUG L.J. 67, 98-100 (2010) (discussing FDA’s authority to enter data-use agreements).

xli 21 U.S.C. §§ 355(k)(4)(A)(ii), 355(k)(4)(D)(i).

xlii *See* Evans, *supra* note 12, at 98-100; *see also* Barbara J. Evans, *The Ethics of Postmarketing Observational Studies of Drug Safety Under Section 505(o)(3) of the Food, Drug, and Cosmetic Act*, 38 AM. J. L. & MED. 577, 599-602 (2012) (discussing the section 355(k)(4) access pathway).

xliii *Id.*

xliiv 21 U.S.C. § 355(k)(4)(A)(i).

xlv *Id.* § 355(k)(4)(F).

xlvi *Id.* § 355(k)(4)(F)(ii)(III).

- xlvi *Id.* § 355(k)(4)(F)(ii)(IV).
- xlviii 21 U.S.C. § 355(k)(3)(C)(1)(II)
- xliv *Id.* § 355-1(b).
- i *Id.* § 355-1(b)(1).
- ii *Id.* § 355-1(b)(1).
- iii *Id.* § 355-1(b)(4).
- iiii *Id.* § 355-1(b)(5).
- lv *Id.* § 355-1(b)(4).
- lv *Id.* § 355-1(b)(5).
- lvi Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936 (codified as amended in scattered sections of 18, 26, 29, 42 U.S.C.).
- lvii 45 C.F.R. pts. 160, 164, subpt. E.
- lviii *Id.* § 164.514(h)(2)(ii).
- lix *Id.* § 164.512(b)(1)(i).
- lx ROSATI ET AL, *supra* note 36, at 7 (discussing the lack of IRB review requirements in HIPAA’s public health exception at 45 C.F.R. § 164.512(b)(1)).
- lxi Barbara J. Evans, *Institutional Competence to Balance Privacy and Competing Values: The Forgotten Third Prong of HIPAA Preemption Analysis*, 46 U.C. DAVIS L. REV. 1175, 1220-23 (2013).
- lxii 21 U.S.C. § 355(k)(4)(B),(G).
- lxiii *Id.* § 355(k)(4)(B).
- lxiv *Id.* § 355(k)(4)(G)(i)(I).
- lxv *Id.*
- lxvi *Id.* § 355(k)(4)(G)(i)(III).
- lxvii *Id.* § 355(k)(4)(G)(ii)(I).
- lxviii *Id.* § 355(k)(4)(G)(ii)(II).
- lxix *Id.* § 355(k)(4)(G)(iii).
- lxx *See id.* § 355(k)(4)(G) (listing certain required contractual privacy protections but not otherwise limiting the FDA’s ability to contract for additional protections); *see also* Deven McGraw, Kristen Rosati & Barbara Evans, *A policy framework for public health uses of electronic health data*, 21 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 18, 21-22 (2012) (noting that FDA’s policies are enforced through contractual agreements with the data partners).
- lxxi *See* McGraw et al., *supra* note 70, at 20-22 (summarizing these policies); *see also* Susan Forrow et al., *The Organizational Structure and Governing Principles of the Food and Drug Administration’s Mini-Sentinel Pilot Program*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 12, 14 (2012); Platt et al., *supra* note 32, at 1.
- lxxii *See* Robb et al., *supra* note 32, at 10 (discussing FDA’s use of a distributed data system model with voluntary participants for Mini-Sentinel).