

SENTINEL INITIATIVE PRINCIPLES AND POLICIES

HIPAA AND COMMON RULE COMPLIANCE IN THE SENTINEL INITIATIVE

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. BloodSCAN is the Sentinel component for safety surveillance of blood products and blood components. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) contract number HHSF223201400030I.

Sentinel Initiative Principles and Policies

HIPAA and Common Rule Compliance in the Sentinel Initiative¹

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¹ This White Paper is produced as a general reference source and is not meant to provide legal advice to any person or entity that receives a copy of the work. The original version of this White Paper for the Mini-Sentinel Pilot was authored in 2011 by the Mini-Sentinel Privacy Panel: Kristen Rosati, Barbara Evans and Deven McGraw. Views expressed here are those of Professor Barbara Evans in her individual capacity and do not reflect views of her employer.

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I. EXECUTIVE SUMMARY

The Food and Drug Administration's ("FDA") Sentinel Initiative is a long-term effort to improve the FDA's ability to identify and assess medical product safety issues. The Sentinel Infrastructure provides routine querying tools and vetted pre-existing electronic healthcare data from multiple sources (called "Sentinel Data") for use by the Sentinel System to monitor the safety and effectiveness of regulated medical products. FDA-Catalyst activities leverage the Sentinel Infrastructure by utilizing the Sentinel Data and supplementing it with data obtained through interventions or interactions with individual and health care providers to conduct research.

This White Paper addresses compliance under the Health Insurance Portability and Accountability Act ("HIPAA")² and the Common Rule³ for data sources participating in the Sentinel Initiative. This White Paper does not address data source compliance with the federal Confidentiality of Substance Use Disorder Patient Record regulations,⁴ or compliance with state health information confidentiality laws and state human subject protection requirements. Data sources participating in the Sentinel Initiative should confirm that their participation complies with other laws that apply to the types of information used or disclosed for the Sentinel Initiative projects.

A. THE USE OF SENTINEL DATA FOR PUBLIC HEALTH PRACTICE

"Public health practice" is the application of existing knowledge and techniques to protect the public's health. Medical product safety surveillance and the evaluation of medical product effectiveness directly support FDA's mission to protect the public's health and fall squarely within public health practice. The HIPAA Privacy Rule⁵ allows access to Sentinel Data for public health practice without individual authorization. Moreover, the Common Rule does not regulate the use of Sentinel Data for public health practice. The Director of the Department of Health and Human Services ("HHS") Office for Human Research Protections ("OHRP") determined in 2010 that the Common Rule does not apply to Sentinel Initiative medical product safety surveillance. (See **Exhibit 1.**) In addition, recent amendments to the Common Rule expressly provide that medical product safety surveillance activities will not be subject to the Common Rule when those amendments take effect (the "Amended Common Rule").⁶

² Pub. L. No. 104-191, 110 Stat. 1936 (1996) (codified as amended at scattered sections of 18, 26, 29, 42 U.S.C.).

³ 45 C.F.R. Part 46.

⁴ 42 C.F.R. Part 2.

⁵ 45 C.F.R. Part 160 and Subparts A and E of Part 164.

⁶ U.S. Dep't of Health & Human Servs. et al, Federal Policy for the Protection of Human Subjects: Final Rule, 82 Fed. Reg. 7149 (Jan. 19, 2017), available at <https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>. On January 22, 2018, HHS delayed the revisions to the Common Rule until July 19, 2018: 83 Fed. Reg. 2885 (Jan. 22, 2018), available at <https://www.gpo.gov/fdsys/pkg/FR-2018-01-22/pdf/2018-00997.pdf>. Because it is unclear when the amended Common Rule will be effective, this paper addresses both the current rule and the final amendments where applicable to the discussion.

B. THE USE OF SENTINEL DATA FOR RESEARCH

Activities under the FDA-Catalyst program (“FDA-Catalyst activities”) in many instances will involve the prospective collection of new data through interactions with research participants, and thus will be human subjects research under the Common Rule. The Common Rule generally requires informed consent from the research participants or Institutional Review Board (“IRB”) waiver of informed consent.

Some of the FDA-Catalyst activities may be in the nature of “public health research,” in that they are studies performed by or for a public health authority to create new generalizable knowledge to improve public health practice in the future. Both the pre-Amended Common Rule and the Amended Common Rule treat public health research like any other human subjects research that is subject to the Common Rule.

However, a new development is that the Amended Common Rule provides an exemption for the use or disclosure of protected health information (“PHI”) that is regulated by HIPAA as research, public health, or health care operations. That means that, as long as the PHI stays within or is transferred to a HIPAA covered entity or a HIPAA business associate, it is exempt from Amended Common Rule regulation. Disclosure of PHI to an outside entity that is not regulated by HIPAA would not be subject to the new exemption.

Applied to FDA-Catalyst activities, research uses of Sentinel Data conducted within HIPAA covered entities will be exempt from the Amended Common Rule. The subsequent disclosure of Sentinel Data to the SOC, the FDA or other non-covered entities will not be eligible for this new HIPAA exemption, but will not be classified as “human subjects” research under the Common Rule if the Sentinel Data are stripped of all “direct” identifiers. Therefore, starting in July 2018—assuming the revised Common Rule goes into effect as planned and assuming the data flow in Sentinel continues as currently structured—the use of Sentinel Data for FDA-Catalyst activities will not be subject to regulation under the Common Rule. However, the clinical study components involving interactions with individuals will continue to be subject to the Common Rule, because the HIPAA exemption applies only to the secondary use of data generated for purposes other than the research protocol, not other research activities.

The HIPAA Privacy Rule itself also may not require IRB review of all FDA-Catalyst activities. The HIPAA Privacy Rule permits use and disclosure for “public health activities” without individual authorization. While “public health research” is not defined, it appears to fall within the scope of public health activities as a public health “investigation.” Nonetheless, because HHS has not published guidance on how it will interpret public health research, and because many FDA-Catalyst activities will involve general non-public health research, this White Paper recommends that use and disclosure of data for FDA-Catalyst activities obtain IRB review and meet the HIPAA requirements of authorization or IRB waiver of authorization.

Finally, FDA-Catalyst research intends to use a central IRB to review all FDA-Catalyst activities. The use of one IRB by multiple institutions is permitted by HIPAA and the Common Rule, and has been increasingly encouraged by federal agencies. Indeed, use of a central IRB is required for multi-site research funded by the National Institutes of Health (“NIH”) and will be required by the Common Rule for most multi-site research by January 2020.

C. SUMMARY OF COMPLIANCE FOR SENTINEL PUBLIC HEALTH PRACTICE, PUBLIC HEALTH RESEARCH AND RESEARCH ACTIVITIES

Table 1 provides a summary of how the HIPAA Privacy Rule, the pre-Amended Common Rule, and the Amended Common Rule treat public health practice, public health research, and general non-public health research. This summary is explained in detail in the Legal Analysis below.

Table 1. Summary of Compliance for Sentinel Public Health Practice, Public Health Research and Research Activities

	HIPAA Privacy Rule	Pre-Amended Common Rule	Amended Common Rule
Public Health Practice <i>The application of existing knowledge and techniques to protect the public's health.</i>	The Privacy Rule does not require individual authorization to disclose PHI to a public health authority for public health activities.	The pre-Amended Common Rule does not define public health practice. Public health agencies and IRBs must infer whether an activity is public health practice by determining that it does not fit into the Common Rule's definition of human subject research.	The Amended Common Rule clarifies that "public health surveillance activities" are not subject to the Common Rule. There is another new exemption where the use of the data will be regulated by HIPAA as public health activity, research, or health care operations.
Public Health Research <i>Studies performed by or for a public health authority to create new generalizable knowledge to improve public health practice in the future.</i>	The HIPAA Privacy Rule does not require individual authorization to disclose PHI to a public health authority for public health activities. While "public health research" is not defined, it arguably is included in "public health activities."	The pre- Amended Common Rule does not recognize a distinction between public health research and other research. When a public health activity fits within the Common Rule's definition of research, the activity is considered research.	The Amended Common Rule does not recognize a distinction between public health research and other research. All public health research is subject to the Common Rule (unless the transfer of data is to an entity regulated by HIPAA).
General Research <i>Research that is not classified as "public health research."</i>	The HIPAA Privacy Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Disclosures of data for non-public health research are not eligible for the HIPAA exemption for disclosures of PHI to a public health authority for public health activities.	The pre- Amended Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.	The Amended Common Rule adopts the same basic definition of human subject research as the pre-2018 Common Rule, but narrows the definition by expressly excluding four activities that are declared not to be research.

II. FACTUAL BACKGROUND

A. THE SENTINEL INITIATIVE

Consistent with its mission to protect and promote the public health, the FDA embarked on the Sentinel Initiative to create an electronic system operating across different data environments—provider electronic health records, health plan claims databases, and other electronic health care data—to monitor medical products approved by the FDA. The Sentinel Initiative has strengthened the FDA's ability to monitor the performance of medical products after approval and improved the FDA's medical product safety surveillance capabilities.

The Sentinel Initiative was required by the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).⁷ Section 905 of FDAAA called for HHS to develop methods to obtain access to disparate electronic health care data and to establish an active post-market risk identification and analysis system that links and analyzes healthcare data from multiple environments.⁸ The law set goals of access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012,⁹ which were met. The law also required the FDA to work closely with partners from public, academic, and private institutions.¹⁰

Mini-Sentinel was a pilot project of the Sentinel Initiative, which provided the foundational work necessary to inform and facilitate the development of a fully operational active surveillance system for monitoring the safety of FDA-regulated medical products (the “Sentinel System”). The Mini-Sentinel pilot was conducted as a collaborative effort by a consortium that included a variety of hospital systems, health plans, universities, and research institutes.

The FDA began transitioning from the Mini-Sentinel phase to the full Sentinel System in September 2014, and the Sentinel System officially launched in February 2016. Under a contract with the FDA, Harvard Pilgrim Health Care Institute operates the Sentinel Operations Center (“SOC”), which administers the Sentinel Initiative activities. The SOC partners with a broad range of “Data Partners” and “Academic Partners,” collectively referred to as “Collaborating Institutions.” The network of Collaborating Institutions provides access to scientific, technical, and organizational expertise, with Data Partners additionally contributing health care data, as noted below.¹¹ Collaborating Institutions receive compensation for their conduct of Sentinel Initiative activities under subcontracts with the SOC.

The Sentinel System is an active surveillance system sponsored by the FDA to monitor the safety and effectiveness of regulated medical products and to better understand their performance in real world contexts, using pre-existing electronic healthcare data from multiple sources. The Sentinel System includes all FDA activities that use the Sentinel Infrastructure to evaluate medical products using observational methodologies.

FDA-Catalyst activities expand FDA's observational methods through combining data included in the Sentinel Infrastructure with direct contact with providers and individuals. FDA-Catalyst activities leverage the Sentinel Infrastructure and other capabilities to answer a wider range of questions than can

⁷ Pub. L. 110-85, 121 Stat. 823 (2007).

⁸ 21 U.S.C. § 355(k)(3).

⁹ *Id.* § 355(k)(3)(B)(ii).

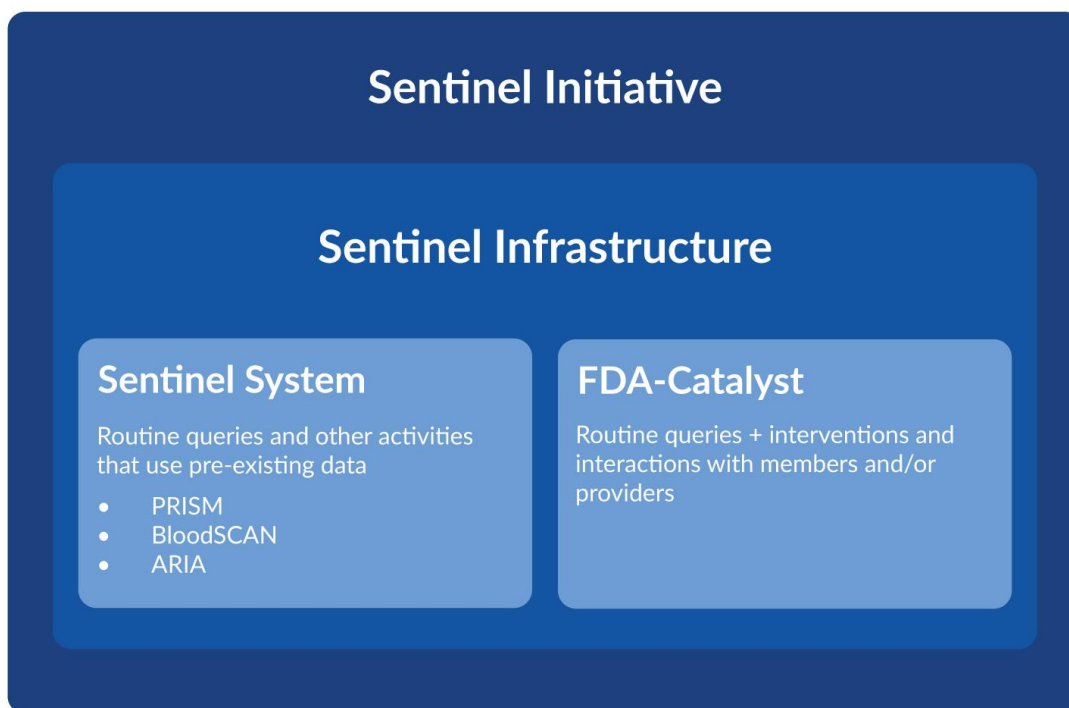
¹⁰ *Id.* § 355(k)(3)-(4).

¹¹ *Id.* § 355(k)(3)(B) & (4)(A). Active Collaborating Institutions are listed on the Sentinel Initiative webpage at <https://www.sentinelinitiative.org/collaborators> (last visited Sept. 20, 2017).

be addressed by the Sentinel System alone. These activities ultimately complement the existing post-market surveillance system.

FDA-Catalyst’s first randomized trial, IMPACT-AFib, is an individually randomized trial that provides educational materials to physicians and their patients, as part of an intervention to increase anticoagulant use for individuals with atrial fibrillation (“AF”) and an increased risk of stroke. The design of this trial provides patient and provider education on stroke prevention to determine if education materials on AF result in increased use of oral anticoagulants for stroke prevention among individuals at risk for stroke. All inclusion criteria, exclusion criteria, and outcomes are determined through claims data, through the Sentinel Initiative’s distributed data approach. The primary outcome assessment is the proportion of AF patients with evidence of at least one oral anticoagulant prescription fill over the course of the 12-month trial. The secondary aims include exploration of the ability to successfully conduct a pragmatic trial to assess the public health impact of the intervention on stroke. This project is the first FDA-Catalyst study conducted using the Sentinel Infrastructure and will inform future interventional studies designed to leverage the Sentinel Infrastructure to utilize existing health care data as part of the study design.

Figure 1. Relationship of Sentinel Initiative Activities



B. DATA FLOW IN THE SENTINEL INITIATIVE

1. Data Flow for Sentinel Public Health Activities

Data containing “direct” identifiers¹² (such as patient names) generally will not flow from Data Partners to the SOC or the FDA. “Indirect” identifiers, including dates of service or geographic codes, may flow for the Sentinel activities.

Data Partners maintain physical and operational control over their data, which are configured in the Sentinel “Common Data Model” that allows uniform queries across different data sources. Data Partners execute analysis programs that are distributed by the SOC and provide the output of these analyses back to the SOC by uploading results to a Federal Information Security Modernization Act (“FISMA”) compliant secure transfer system. Whenever possible, the output the Data Partners share contains only summary or aggregate information, such as counts of health plan members categorized by: (1) the presence or absence of a particular health condition; (2) exposure to a particular medical product; (3) the presence or absence of a particular health outcome; and (4) demographic characteristics.

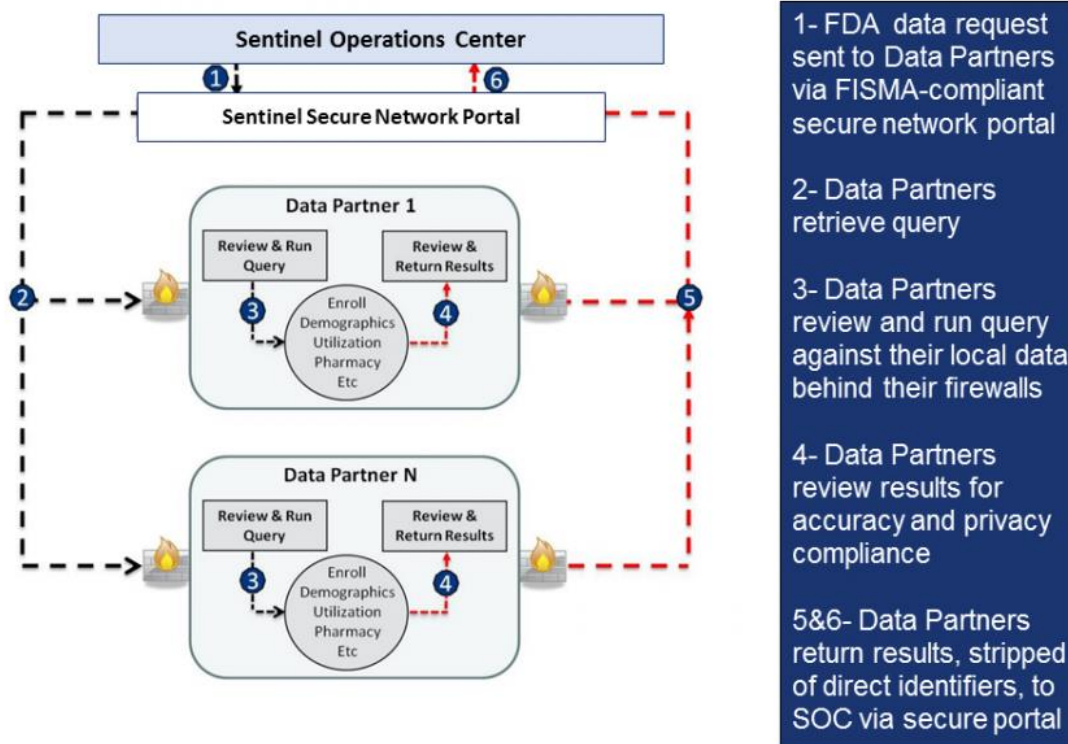
When person-level information is provided, it is stripped of all direct identifiers. For example, in order to confirm an adverse drug reaction, a Data Partner may provide clinical data about a particular individual; this data will exclude name and contact information, but may include dates of service. As another example, when medical charts are needed to perform chart reviews, the SOC will receive only charts that are stripped of all direct identifiers (but include dates related to the patient, such as birth date and dates of service). The SOC also may use various electronic tools that will ask for person-level data to be returned in response to queries by the SOC on behalf of the FDA. For example, the SOC plans to use a tool called Patient Episode Profile Retrieval (“PEPR”) as a cost-effective alternative to reviewing full charts. PEPR will give the SOC the option of requesting that a Data Partner include “patient episode profiles” along with the aggregated data the Data Partner provides to the SOC in response to a query. A “patient episode profile” is a patient-level summary of information, such as encounters, ICD-9 codes, and procedure codes, relating to the patient during a particular time period. The more limited PEPR data may obviate the need for the SOC to obtain the patient’s full chart. Data that the SOC receives through PEPR will exclude all direct identifiers.

If permitted by the SOC contracts with Data Partners, the SOC also may re-disclose the data it receives from Data Partners to Collaborating Institutions in order to obtain expertise or support in carrying out Sentinel System activities. The SOC also may disclose this data to other subcontractors that are not Collaborating Institutions for the same purposes, such as to support a review of laboratory result data in the Sentinel System. Such data do not include any direct identifiers.

¹² “Direct” identifiers are those identifiers excluded in the creation of Limited Data Sets under HIPAA. Specifically, “direct” identifiers are the following identifiers about the individual or about relatives, employers, or household members of the individual: (i) Names; (ii) Postal address information (other than town or city, State, and 5-digit zip code); (iii) Telephone numbers; (iv) Fax numbers; (v) Electronic mail addresses; (vi) Social security numbers; (vii) Medical record numbers; (viii) Health plan beneficiary numbers; (ix) Account numbers; (x) Certificate/license numbers; (xi) Vehicle identifiers and serial numbers, including license plate numbers; (xii) Device identifiers and serial numbers; (xiii) Web Universal Resource Locators (URLs); (xiv) Internet Protocol (IP) address numbers; (xv) Biometric identifiers, including finger and voice prints; and (xvi) Full face photographic images and any comparable images.” 45 C.F.R. § 164.514(e)(2).

The data flows for Sentinel public health activities (medical product surveillance and medical product effectiveness evaluation activities) are reflected in **Figure 2**:

Figure 2. Sentinel Initiative Distributed Data Querying System



It is possible that some of the aggregate data flowing from the Data Partners to the SOC for Sentinel public health activities will technically be PHI under HIPAA, because the information reported may include dates of service or geographic codes (data elements that are “indirect” HIPAA identifiers), or because the information may represent “small cells” in which the diagnosis is sufficiently unique to be able to identify an individual if paired with other available information. In addition, it is possible that the FDA could request patient-identifiable data, with agreement from the Data Partners, if needed for a compelling public health purpose. Because data that is classified as PHI may flow to the SOC or the FDA for Sentinel public health activities, we evaluate in the discussion below whether this complies with the HIPAA Privacy Rule.

In addition, patient-level data may flow from HIPAA covered entities, such as hospitals or clinics, to the Collaborating Institutions to confirm the validity of adverse event drug safety signals. This patient-level data may include PHI. Collaborating Institutions may provide scientific, technical, and organizational expertise, including leading workgroups or otherwise providing expertise. The SOC may re-disclose data it receives from Data Partners to Collaborating Institutions for these purposes. Such data will not include any direct identifiers. For example, a Collaborating Institution might ask for portions of the medical record from a treating health care provider to determine if the drug in question was administered before or after the adverse clinical event occurred, or to determine whether other patient conditions may have resulted in the adverse clinical event observed. Another example involves state immunization registries: to evaluate the safety of immunizations, Collaborating Institutions may seek information from immunization registries regarding whether individuals have received certain immunizations. Because PHI

may flow to the Collaborating Institutions for Sentinel public health activities, we evaluate below whether this would comply with the HIPAA Privacy Rule.

Additionally, Data Partners may be asked to gather information from other sources for Sentinel public health activities. This may include information that is already routinely collected by other sources, such as information in health care data registries for particular diseases or medical procedures (“external source data”). External source data will not be added to the Data Partner’s Common Data Model without individual consent, and may be used and disclosed by the Data Partner only for the specific activities for which they are collected. As with other data disclosed for Sentinel purposes, Data Partners will disclose external source data to the SOC and the FDA in summary or aggregate form where possible, or stripped of direct identifiers where patient-level data is necessary.

2. Data Flow for FDA-Catalyst Activities

The SOC will often, but not always, serve as the lead research site in FDA-Catalyst projects; in some cases, other Collaborating Institutions participating in FDA-Catalyst will serve as the lead research site.

As with the Sentinel public health activities described above, directly identifiable data will not flow to the SOC, other Collaborating Institutions, or the FDA for FDA-Catalyst activities. Data Partners that choose to participate in FDA-Catalyst activities will maintain physical and operational control over their data. The SOC will send requests to conduct FDA-Catalyst activities to Data Partners. The Data Partners will conduct the requested FDA-Catalyst activities behind their firewalls, such as the outreach to providers and patients for the IMPACT-AFib study described above. The Data Partners will provide the results to the SOC by uploading those results to a FISMA-compliant secure transfer system. When possible, the results they share will contain only summary or aggregate information. When person-level information is provided to the SOC, the Data Partner will strip all direct identifiers from the information. For example, as described above, medical charts or PEPR data will exclude all direct identifiers.

Collaborating Institutions may provide scientific, technical, and organizational expertise for FDA-Catalyst activities, including leading workgroups or otherwise providing expertise. The SOC may re-disclose data it receives from Data Partners to Collaborating Institutions for these purposes. Such data will not include any direct identifiers.

As in the public health activities, it is possible that some of the aggregate data flowing from the Data Partners to the SOC for FDA-Catalyst activities will technically be PHI under HIPAA, because the information reported may include dates of service or geographic codes (data elements that are “indirect” HIPAA identifiers), or because the information may represent “small cells” in which the diagnosis is sufficiently unique to be able to identify an individual if paired with other available information. Because data that is classified as PHI may flow to the SOC, the Collaborating Institutions, or the FDA for FDA-Catalyst activities, we evaluate in the discussion below what use and disclosure of PHI for FDA-Catalyst activities complies with the HIPAA Privacy Rule.

Finally, by nature of the approach for FDA-Catalyst activities, there will be collection of information from health care providers or health plans that are not Data Partners, but which are participating in FDA-Catalyst activities (“primary source data”). Additionally, Data Partners may be asked to gather information from other sources for FDA-Catalyst activities. This may include information that is already routinely collected by other sources, such as information in health care data registries for particular diseases or medical procedures (“external source data”). Primary source data and external source data will not be added to the Data Partner’s Common Data Model without individual consent, and may be used and disclosed only for the specific FDA-Catalyst activities for which they are collected.

III. LEGAL ANALYSIS

A. APPLICABILITY OF LAWS

1. HIPAA

HIPAA, the Health Information Technology for Economic and Clinical Health Act (“HITECH Act”)¹³, and the regulations that implement HIPAA and HITECH¹⁴ (collectively referred to in this White Paper as “HIPAA”), govern organizations or people that are “covered entities” or “business associates.” Covered entities are defined to include:

- Health care providers that transmit health information electronically in connection with “standard transactions,” such as electronic claims for payment submitted to health plans;
- Health plans, including health insurance companies, HMOs, the Medicare and Medicaid programs, employee welfare benefit plans (group health plans), and any other individual or group plan “that provides, or pays the cost of, medical care”; and
- Health care clearinghouses (organizations that assist health care providers and health plans in conducting standard transactions, such as third-party billing companies).¹⁵

HIPAA also applies to “business associates” of covered entities.¹⁶ A business associate is an organization or person that creates, receives, maintains or transmits PHI on behalf of a covered entity to carry out its HIPAA-covered functions (such as billing), or uses PHI to perform certain services for the covered entity (such as legal services).¹⁷

2. Common Rule

The federal Common Rule is a set of regulations that govern federally-funded biomedical and behavioral “research” that involves “human subjects.”¹⁸ “Research” is defined as a systematic investigation designed to develop or contribute to generalizable knowledge.¹⁹ “Human subjects” are living individuals about whom a researcher obtains identifiable information or where data is collected through interaction

¹³ Title XIII of Division A and Title IV of Division B of the American Recovery and Reinvestment Act of 2009, Pub. L. 111-5.

¹⁴ 45 C.F.R. Parts 160, 162 and 164.

¹⁵ 45 C.F.R. § 160.103 (definitions of “covered entity,” “health care provider,” “health plan” and “health care clearinghouse”).

¹⁶ *Id.* § 164.104(b).

¹⁷ *Id.* § 160.103 (definition of “business associate”).

¹⁸ 45 C.F.R. Part 46.

¹⁹ *Id.* § 46.102(d) (“*Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.”).

with the individuals.²⁰ In other words, an entity does not conduct “human subjects research” under the HHS regulations if the data was not collected for currently proposed research and the investigator cannot readily ascertain the identity of the participants, or there is no interaction or intervention with individuals.

An organization must comply with the federal Common Rule if human subjects research is conducted or funded by any federal department or agency that has adopted the Common Rule.²¹ The Common Rule has been adopted by 15 federal departments and agencies, including HHS.²² Because the FDA is an agency within HHS, research funded by the FDA must comply with the Common Rule.²³ This will include FDA-Catalyst activities.

²⁰ *Id.* § 46.102(f) (“*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.”).

²¹ *Id.* § 46.101.

²² HHS, OHRP, REGULATIONS: FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS (‘COMMON RULE’) (last reviewed Mar. 18, 2016), <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html> (last visited Sept. 20, 2017).

²³ HHS, OHRP, REGULATIONS: FOOD & DRUG ADMINISTRATION (last reviewed Mar. 18, 2016), <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/fda/index.html> (stating that FDA is an agency of HHS) (last visited Sept. 20, 2017); Barbara J. Evans, *FDA Sentinel Initiative Meeting Series: Issue Brief: Legal Issues in Active Medical Product Surveillance*, at 3 (Mar. 2010), <https://www.brookings.edu/wp-content/uploads/2012/04/Panel-3-Issue-Brief.pdf> (concluding that Common Rule would apply to FDA-funded research) (last visited Sept. 20, 2017); *see also* FDA, FDA FIELD MANAGEMENT DIRECTIVES: REVIEW OF HUMAN SUBJECT RESEARCH (Apr. 12, 2005) (“FDA has provided assurance to [HHS] that all activities related to human subject research will . . . comply with HHS regulations for the protection of human research subjects . . .”); NATL. RESEARCH COUNCIL (US) COMMITTEE ON THE USE OF THIRD PARTY TOXICITY RESEARCH WITH HUMAN RESEARCH PARTICIPANTS, INTENTIONAL HUMAN DOSING STUDIES FOR EPA REGULATORY PURPOSES: SCIENTIFIC AND ETHICAL ISSUES n.3 (2004), *available at* <https://www.ncbi.nlm.nih.gov/books/NBK215883/> (“FDA is bound to DHHS regulations [the Common Rule] when it conducts its own research.”).

The Common Rule was amended on January 19, 2017.²⁴ The revised rule has a present effective date of July 19, 2018,²⁵ except for the requirement to use a centralized IRB for multi-site research, which has an effective date of January 20, 2020.²⁶

The revised rule, which we call the Amended Common Rule in this White Paper, will affect several of the standards discussed in this White Paper, including the requirements for informed consent, waiver of informed consent, activities to prepare for research and for patient recruitment, and use of a centralized IRB. This paper refers to the current Common Rule that has been in effect since 1991, as the pre-Amended Common Rule.

3. FDA Regulations

The FDA regulates certain human subjects research,²⁷ but the applicability of the FDA's regulations is limited.²⁸ The FDA's regulations at 21 C.F.R. Parts 50 and 56 replicate many of the Common Rule's human subject protections, but define "human subject"²⁹ differently than the Common Rule. The FDA regulations also apply only to clinical investigations.³⁰ Because these regulations likely will not apply to

²⁴ 82 Fed. Reg. 7149 (Jan. 19, 2017).

²⁵ 83 Fed. Reg. 2885 (Jan. 22, 2018).

²⁶ 82 Fed. Reg. at 7149. HHS's delay of revisions to the Common Rule until July 19, 2018, does not affect the January 20, 2020 compliance date for use of a centralized IRB for multi-site research. See 83 Fed. Reg. at 2886 ("This interim final rule does not delay the compliance date for the cooperative research provision of the 2018 requirements (§ .114(b)), which remains January 20, 2020.").

²⁷ 21 C.F.R. Parts 50 and 56.

²⁸ See Barbara J. Evans, *The Limits of FDA's Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing*, 70 FOOD DRUG LAW J. 259 (2015) ("FDA's legal authority as a research regulator is narrowly circumscribed, because FDA's authority to regulate research is merely an incident of its authority to regulate medical products such as drugs and devices. This limitation is evident in Part 812 [governing investigational device exemptions]. As a general rule, Part 812 allows FDA to regulate investigations of devices, as opposed to regulating investigations that merely use devices as tools to study other things.").

²⁹ 21 C.F.R. §§ 50.3(g) and 56.102(e) (defining "human subject" as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control" for purposes of FDA's informed consent, IRB review, and investigational new drug regulations); see also 21 C.F.R. § 812.3(p) (further including persons "on whose specimen an investigational device is used" within the definition of "subjects" protected by FDA's investigational device exemption regulations).

³⁰ *Id.* § 56.101 ("This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) [exemption for new drugs for investigational use] and 520(g) [exemption for devices for investigational use] of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration . . ."); *id.* § 50.1(a) (stating same). A "clinical investigation" is "any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) [exemption for new drugs for investigational use] or 520(g) [exemption for devices for investigational use] of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include

the type of research that will be conducted in the FDA-Catalyst activities, this White Paper does not address those standards.

B. HIPAA COMPLIANCE

1. Sentinel System Public Health Activities

a. Disclosure of PHI for Public Health Activities Permitted without Individual Authorization

The provision of Sentinel Data to the FDA, the SOC, and the Collaborating Institutions to support Sentinel public health activities is permitted under the HIPAA Privacy Rule without patient authorization. The HIPAA Privacy Rule permits covered entities to disclose PHI for a variety of public health activities, including to:

[A] public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions; or, at the direction of a public health authority, to an official of a foreign government agency that is acting in collaboration with a public health authority.³¹

The FDA is a “public health authority” under HIPAA, which is defined as:

[A]n agency or authority of the United States, a State, a territory, a political subdivision of a State or territory, or an Indian tribe, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.³²

The SOC and its subcontractors (the Collaborating Institutions, and other subcontractors retained by the SOC to carry out Sentinel System activities) also are functioning as “public health authorities,” because they are acting under contract with or under a grant of authority from the FDA. The SOC is performing its functions under contract with the FDA. Moreover, even though the Collaborating Institutions do not have a direct contract with the FDA, the FDA issued a letter to the Sentinel Operations Center in 2010 explaining that both the Sentinel Operations Center and its subcontractors are acting under a grant of

experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous for purposes of this part.” *Id.* §§ 56.102(c) (emphasis in original), 50.3(c). A “test article” is “any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.” *Id.* §§ 56.102(l), 50.3(j).

³¹ 45 C.F.R. § 164.512(b)(1)(i).

³² *Id.* § 164.501 (definition of “public health authority”) (emphasis added).

authority from the FDA. (See **Exhibit 3.**) This will extend to other subcontractors retained by the SOC to assist in carrying out Sentinel System activities, even if they are not Collaborating Institutions.

The release of PHI to the FDA for purposes of medical product safety surveillance and medical product efficacy is for the “conduct of public health surveillance” purposes, as contemplated by the rule, because those activities fall squarely within the FDA’s regulatory authority.³³ Where a disclosure of PHI is to a public health authority for the conduct of public health surveillance, the HIPAA Privacy Rule does not require the covered entity to obtain individual authorization for the disclosure.³⁴ Thus, data sources release PHI to the FDA, the SOC, the Collaborating Institutions, and other SOC subcontractors as “public health authorities” for the purpose of the Sentinel System activities.³⁵

The HIPAA Privacy Rule suggests that research conducted by a public health authority, with the principal aim of improving public health practice in the future, is also a “public health activity” permitted without individual authorization. The Privacy Rule does not define “public health practice” or “public health research” and draws no distinction between the two. Instead, the Privacy Rule provides an exception to HIPAA’s individual authorization requirement when covered entities disclose data for certain “public health activities.”³⁶ This exception lets HIPAA covered entities disclose PHI (even in identifiable form) without individual authorization to “public health authorities”³⁷—including state and federal public health agencies like FDA, their employees, and contractors³⁸—for “public health surveillance, public health investigations, and public health interventions.”³⁹ This use of the word “investigations” strongly suggests that covered entities may disclose data, without individual authorization, for legally authorized public health research as well as public health practice.⁴⁰ However, we understand that many of the FDA-Catalyst activities may be in the nature of general non-public health research that is not eligible for this exception. Therefore, access to Sentinel Data for use in FDA-Catalyst activities generally will need to comply with HIPAA’s other requirements (such as obtaining individual authorization or IRB waiver of authorization), rather than relying on the public health activities exception.

However, as we discuss in Section III.C.1 below, the Common Rule does make a distinction between public health practice and public health research, and public health research requires IRB review under the Common Rule.

³³ “[T]he Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA.” FDA, SAFETY: HIPAA COMPLIANCE FOR REPORTERS TO FDA MEDWATCH (last updated Mar. 25, 2016), <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085589.htm> (last visited Sept. 20, 2017) (citing HHS Office for Civil Rights Guidance Explaining Significant Aspects of the Privacy Rule at page 28).

³⁴ 45 C.F.R. § 164.512(b)(1)(i).

³⁵ The internal use of PHI by the Collaborating Institution would similarly be permitted under HIPAA. 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 LAW JOURNAL 67, 112 (2009).

³⁶ 45 C.F.R. § 164.512(b)(1)(i).

³⁷ *Id.*

³⁸ *Id.* § 164.501 (definition of “public health authority”).

³⁹ *Id.* § 164.512(b)(1)(i).

⁴⁰ Barbara J. Evans, *Much Ado about Data Ownership*, 25 HARVARD J. LAW & TECH 69, 118 (2011).

b. Verification of Identity and Authority to Request PHI

To disclose PHI to the FDA or an entity acting under a contract or other grant of authority from the FDA, data sources must confirm the recipient's identity and that the recipient has the legal authority to request the PHI.⁴¹ A covered entity is entitled to rely on written confirmation on FDA letterhead that the SOC and the Collaborating Institutions are acting on behalf of the FDA, and that they have the legal authority to request PHI for Sentinel System activities.⁴² As noted above, the FDA issued a letter to the Sentinel Coordinating Center explaining that both the Sentinel Coordinating Center and the Collaborating Institutions are acting under a grant of authority from the FDA, pursuant to the legal authority provided by the FDAAA. (See **Exhibit 3**.) In other words, the data sources are not expected to make their own independent inquiry into whether queries from the FDA, the SOC, the Collaborating Institutions or other SOC subcontractors for Sentinel System activities serve a legally authorized public health purpose.

c. Data Use Agreements Are Not Required for Disclosure to a Public Health Authority for Public Health Activities

Where the disclosure of PHI is to a public health authority for public health activities, the HIPAA Privacy Rule does not require the recipient to sign a Data Use Agreement ("DUA"). The HIPAA Privacy Rule does permit a covered entity to release a Limited Data Set (partially de-identified data) for public health, research and health care operations purposes, as long as the covered entity first obtains a DUA with the recipient of the Limited Data Set.⁴³ This rule permits the release of a Limited Data Set to entities that are

⁴¹ *Id.* § 164.514(h)(1)(i).

⁴² *Id.* § 164.514(h)(2)(ii)(C) (allowing a covered entity, when making disclosure to a person acting on behalf of a public official, to rely on "a written statement on appropriate governmental letterhead that the person is acting under the government's authority or other evidence or documentation of the agency, such as a contract for services ... that establishes that the person is acting on behalf of the public official"; *see also id.* § 164.514(h)(2)(iii)(A) (permitting a covered entity to rely on the written statement of a public agency regarding the legal authority under which it is requesting PHI, or an oral statement if a written statement is impracticable). The Preamble to the Privacy Rule explained further: "For most disclosures, verifying the authority for the request means taking reasonable steps to verify that the request is lawful under this regulation.... Where the person requesting the protected information is a public official, covered entities must verify the identity of the requester by examination of reasonable evidence, such as a written statement of identity on agency letterhead, an identification badge, or similar proof of official status. . . . Similarly, covered entities are required to verify the legal authority supporting the request by examination of reasonable evidence, such as a written request provided on agency letterhead that describes the legal authority for requesting the release. . . . In some circumstances, a person or entity acting on behalf of a government agency may make a request for disclosure of protected health information under these subsections. . . . For example, public health agencies may contract with a nonprofit agency to collect and analyze certain data. . . . In such cases, the covered entity is required to verify the requestor's identity and authority through examination of reasonable documentation that the requestor is acting on behalf of a government agency. . . . Reasonable evidence includes a written request provided on agency letterhead that describes the legal authority for requesting the release and states that the person or entity is acting under the agency or authority." 65 Fed. Reg. 82461, 82547 (Dec. 28, 2000).

⁴³ 45 C.F.R. § 164.514(e).

not “public health authorities” under HIPAA, but that are using the Limited Data Set for public health purposes. However, if the disclosure of PHI is to a “public health authority,” that disclosure does not need to be limited to a Limited Data Set, nor does it require a DUA. Rather, covered entities may release fully-identifiable PHI to public health authorities.⁴⁴

However, some Data Partners have requested the SOC to sign DUAs, which the SOC has agreed to do. An advantage of disclosing Limited Data Sets pursuant to a DUA is that such disclosures do not need to be included in an “accounting” of disclosures under HIPAA, whereas disclosures without patient authorization for public health activities must be included.⁴⁵ HIPAA gives an individual the right to request and receive an accounting of disclosures of PHI made by the covered entity or its business associates within the previous six years, except for certain excluded categories of disclosures, including disclosures of Limited Data Sets pursuant to a DUA or disclosures pursuant to an individual’s authorization.⁴⁶

d. Compliance with Minimum Necessary Standard

HIPAA covered entities and business associates must observe the “minimum necessary standard” in releasing PHI for public health purposes.⁴⁷ This simply means that a covered entity must make reasonable efforts to limit the information to the minimum amount of information that is necessary to accomplish the intended purpose of the disclosure,⁴⁸ with some limited exceptions not relevant here.⁴⁹ A covered entity may not disclose the entire medical record unless there is a specific justification for doing so.⁵⁰

Under the HIPAA Privacy Rule, a covered entity may rely on a public health authority’s determination that the data requested are the minimum necessary data that the agency needs to fulfill the purpose of its request.⁵¹ When the FDA (or the SOC or Collaborating Institutions acting on behalf of FDA) sends a query to a covered entity, Sentinel System policies require the request to be limited to what is required to evaluate the medical product safety and effectiveness. Covered entities thus may rely on these public health authority requests as being limited to the minimum amount of PHI necessary for the Sentinel System activities.

⁴⁴ *Id.* § 164.512(b)(1).

⁴⁵ *Id.* § 164.528(a)(1).

⁴⁶ *Id.*

⁴⁷ *Id.* § 164.502(b).

⁴⁸ 45 C.F.R. § 164.502(b)(1).

⁴⁹ *Id.* § 164.502(b)(2).

⁵⁰ *Id.* § 164.514(d)(5).

⁵¹ *See id.* § 164.514(d)(3)(iii)(A) (“A covered entity may rely, if such reliance is reasonable under the circumstances, on a requested disclosure as the minimum necessary for the stated purpose when: (A) Making disclosures to public officials that are permitted under § 164.512, if the public official represents that the information requested is the minimum necessary for the stated purpose.”).

e. Sale of PHI

The HIPAA Privacy Rule prohibits the “sale” of PHI, including Limited Data Sets.⁵² “Sale” is defined as indirect and direct remuneration from or on behalf of the recipient of PHI “in exchange for” the PHI, without the individual’s authorization.⁵³ However, the regulations contain several exceptions under which a covered entity is permitted to receive remuneration for disclosures, including disclosures for public health activities.⁵⁴

The Collaborating Institutions are not receiving compensation “in exchange for” PHI. The Office for Civil Rights (“OCR”) commentary on this issue demonstrates that payment for services rendered—even if those services involve the provision of PHI—will not be treated as the “sale” of PHI, such as funding received to conduct research or government programs. Rather, the prohibition applies where the covered entity or business associate *primarily* is being compensated to supply PHI. The OCR explained:

[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. . . .

. . . 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).⁵⁵

Here, Collaborating Institutions will be compensated for the services they provide to implement the Sentinel System activities, not for the PHI they provide to support those activities.

⁵² *Id.* § 164.502(a)(5)(ii). The prohibition on sale applies to Limited Data Sets. Because Limited Data Sets may include indirect identifiers, such as dates related to patients and geographic designations, Limited Data Sets are technically PHI. As PHI, Limited Data Sets are subject to the rule. See 78 Fed. Reg. 5565, 5609 (Jan. 25, 2013) (“Disclosures of health information that has been de-identified in accordance with the Privacy Rule at § 164.514(b)-(d) are not subject to the remuneration prohibition as such information is not protected health information under the Rule.... [However, we] decline to completely exempt limited data sets from these provisions as, unlike de-identified data, they are still protected health information.”)

⁵³ 45 C.F.R. § 164.502(a)(5)(ii).

⁵⁴ 45 C.F.R. § 164.502(a)(5)(ii)(2)(i) (permitting remuneration for disclosures of PHI and Limited Data Sets for public health purposes).

⁵⁵ 78 Fed. Reg. at 5606-07.

2. FDA-Catalyst Research Activities

Some of the FDA-Catalyst activities may be in the nature of public health research, done by or for the FDA with the primary aim of improving the FDA’s public health practice in the future. Access to Sentinel Data for such studies arguably would be eligible for HIPAA’s exception for “public health activities.” However, many FDA-Catalyst activities may be in the nature of general research that aims to produce generalizable knowledge to improve health care and patient treatment, not public health practice. For this reason, the FDA has determined that it will treat FDA-Catalyst activities as general research. Moreover, some Data Partners may determine as a matter of policy to treat all research—including public health research—as needing to meet the HIPAA Privacy Rule requirements related to research. This section thus discusses the HIPAA rules related to research activities.

a. Requirements for Use and Disclosure of PHI for Research

The HIPAA Privacy Rule defines “research” as “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”⁵⁶ Under the HIPAA Privacy Rule, covered entities may use PHI internally for research or disclose PHI externally to third parties for research (with the exception of public health investigations, described in the section immediately above), only if the requirements of at least one of the following HIPAA rules are met:⁵⁷

- The research subject or the subject’s authorized representative has signed a written HIPAA authorization (or an informed consent document that integrates all HIPAA authorization requirements);⁵⁸
- An IRB has waived the requirement for authorization;⁵⁹
- The research involves only “de-identified” data;⁶⁰
- The research uses or discloses a Limited Data Set and the covered entity has a DUA in place with the recipient of the Limited Data Set;⁶¹
- The activities are only to prepare for research and required representations are obtained from the researchers;⁶²
- The use or disclosure is for patient recruitment purposes, within certain limits;⁶³
- The research involves only the information of decedents and required representations are obtained from the researchers;⁶⁴

⁵⁶ 45 C.F.R. § 164.501 (definition of “research”).

⁵⁷ *Id.* § 164.512(i) (general rules for use and disclosure of patient information for research). Other HIPAA rules are cited as applicable.

⁵⁸ *Id.* § 164.508.

⁵⁹ *Id.* § 164.512(i).

⁶⁰ *Id.* § 164.514(a)-(b).

⁶¹ 45 C.F.R. § 164.514(c).

⁶² *Id.* § 164.512(i).

⁶³ *Id.* § 164.506 (treatment or health care operations).

⁶⁴ *Id.* § 164.512(i).

- The disclosure of the PHI is required by law;⁶⁵ or
- The research is “grandfathered” under the HIPAA rules.⁶⁶

The HIPAA rules apply both to internal use (including employees accessing, collecting, or otherwise using PHI) and to access by or disclosure to third parties outside of the HIPAA covered entity. This section of the White Paper discusses the six HIPAA rules most likely to be utilized during FDA-Catalyst research: (1) disclosure pursuant to a written HIPAA authorization signed by the research participant; (2) disclosure pursuant to an IRB waiver of HIPAA authorization; (3) disclosure of de-identified information; (4) disclosure of a Limited Data Set pursuant to a DUA; (5) disclosure to prepare for research; and (6) disclosure for patient recruitment for research.

(1) Individual Authorization

A HIPAA authorization form for use or disclosure of PHI for research purposes must include a number of items:⁶⁷

- A specific and meaningful description of the PHI to be used or disclosed in the research (such as the participant’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 use or disclosure (such as the Data Partner and the participant’s other 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 (if applicable), and HHS);
- A description of the specific research protocol or study;
- 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 participant’s right to revoke the authorization in writing and a description of how to do so;
- A statement that the participant 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 participant 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 participant signing the authorization. If the individual will not be allowed to participate in a 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 re-disclosure by the recipient and no longer be protected by the federal privacy rule;⁶⁸

⁶⁵ *Id.* § 164.512(a).

⁶⁶ 45 C.F.R. § 164.512(i).

⁶⁷ *Id.* § 164.508.

⁶⁸ A reference that the recipient’s use of PHI is governed by the informed consent is permissible.

- If the participant will not be given access to medical records during the study, a statement that the participant 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 participant's signature and the date of signature; and
- If the authorization is executed by a personal representative of the participant, a description of that person's authority to act for the participant.

A copy of the signed authorization must be given to the participant.

Under the 2013 revisions to the HIPAA rules, an authorization may seek permission to use or disclose PHI for future research, as long as the authorization adequately describes the future research purposes "such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research."⁶⁹ The OCR expressly provided covered entities with substantial flexibility in determining appropriate language to accomplish this.⁷⁰ This changes the OCR's previous interpretation that a HIPAA authorization could not seek permission to use or disclose PHI for future unspecified research, which conflicted with the Common Rule.⁷¹

However, if the HIPAA authorization for future research is combined with a HIPAA authorization to participate in a clinical trial, the HIPAA authorization for future research must be an "opt-in" (either by

⁶⁹ 78 Fed. Reg. 5565, 5612-13 (Jan. 25, 2013) ("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 research purposes must adequately describe such purposes such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research. This could include specific statements with respect to sensitive research to the extent such research is contemplated. However, we do not prescribe specific statements in the Rule. We agree that it is difficult to define what is sensitive and that this concept changes over time. We also agree with commenters that this approach best harmonizes with practice under the Common Rule regarding informed consent for future research, and allows covered entities, researchers and Institutional Review Boards to have flexibility in determining what adequately describes a future research purpose depending on the circumstances. We have consulted with Office for Human Research Protections (OHRP) and the FDA on this approach to ensure consistency and harmonization with the HHS and FDA human subjects protections regulations, where appropriate.

"With respect to commenters that stated it is impossible for individuals to be truly informed about future research, we note that we are aligning with existing practice under the Common Rule in regard to informed consent and still require that all required elements of a authorization be included in an authorization for future research, even if they are to be described in a more general manner than is done for specific studies.

"Pursuant to this modified interpretation, covered entities that wish to obtain individual authorization for the use or disclosure of protected health information for future research may do so at any time after the effective date of this final rule. Alternatively, covered entities may continue to use only study-specific authorizations for research if they choose.").

⁷⁰ *Id.*

⁷¹ 45 C.F.R. § 164.508; 21 C.F.R. § 50.25; 45 C.F.R. § 46.116; *see also* OHRP, RESEARCH REPOSITORIES, DATABASES, AND THE HIPAA PRIVACY RULE (NIH July 2004), available at http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf; OHRP AND NIH, INSTITUTIONAL REVIEW BOARDS AND THE HIPAA PRIVACY RULE 11-12 (Aug. 15, 2003), at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf.

check-box, separate signature, or separate form). A participant may be required to sign a HIPAA authorization to use and disclose PHI for the particular clinical trial, as a condition of participating in the clinical trial.⁷² On the other hand, a clinical trial participant cannot be required to sign an authorization to use PHI for future research as a condition of participating in the clinical trial, so the individual must be given the opportunity to say “no” to the future research.⁷³ If the HIPAA authorization requirements are integrated into the informed consent document (rather than being a separate form), the informed consent document would need to provide the “opt-in” for future research.

(2) IRB Waiver of HIPAA Authorization

If it is not feasible to get research participants’ authorization—which is fairly typical in “Big Data” research where it will not be feasible to contact thousands or even millions of individuals for authorization—researchers may ask an IRB to waive the HIPAA authorization requirement.

To have the IRB grant this request, the researcher must demonstrate, and the IRB must document, three things:

1. 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;
2. The research could not practicably be conducted without the waiver or alteration of authorization; and
3. The research could not practicably be conducted without access to and use of information identifying the participants.⁷⁴

⁷² The Privacy Rule permits a covered entity to require an individual to sign an authorization to use or disclose the individual’s PHI as a condition of receiving treatment that is part of a clinical trial. 45 C.F.R. § 164.508(b)(4)(i).

⁷³ 45 C.F.R. § 164.508(b)(3) (“Compound authorizations. An authorization for use or disclosure of protected health information may not be combined with any other document to create a compound authorization, except as follows: (i) An authorization for the use or disclosure of protected health information for a research study may be combined with any other type of written permission for the same or another research study. This exception includes combining an authorization for the use or disclosure of protected health information for a research study with another authorization for the same research study, with an authorization for the creation or maintenance of a research database or repository, or with a consent to participate in research. Where a covered health care provider has conditioned the provision of research-related treatment on the provision of one of the authorizations, as permitted under paragraph (b)(4)(i) of this section, any compound authorization created under this paragraph must clearly differentiate between the conditioned and unconditioned components and provide the individual with an opportunity to opt in to the research activities described in the unconditioned authorization.”); *see also* 78 Fed. Reg. at 5609-5611 (interpreting compound authorization requirements in research).

⁷⁴ 45 C.F.R. § 164.512(i).

If researchers are able to collect HIPAA authorization from the participants for some purposes but not others, the researchers can ask the IRB for a partial waiver or alteration of the authorization. For example, researchers could ask the IRB to waive authorization for the initial review of records to determine which patients may be appropriate participants (but not a waiver for enrolling those patients in a clinical trial). Another example is that researchers could ask the IRB to approve verbal authorization if the contact with the participants will be by phone.

(3) De-Identified Data

The HIPAA Privacy Rule protects all information that could identify a covered entity's patients or plan members. However, information that has been de-identified pursuant to the HIPAA de-identification rules is no longer protected by HIPAA.⁷⁵ HIPAA permits two ways to "de-identify" information before it is used or released for research:⁷⁶

First, the covered entity can remove or code all of the "identifiers" in the information. These identifiers include all of the following data about individuals and their family members, household members, or employers:

- 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.

If the covered entity has actual knowledge that, even with these identifiers removed or coded, 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. For example, the information may

⁷⁵ *Id.* § 164.502(d). If information is re-identified, it must then be treated as PHI once again. *Id.* Information that is coded may not be disclosed with the code. *Id.*

⁷⁶ *Id.* § 164.514(a)-(b).

represent “small cells,” in which a diagnosis or condition (such as a rare type of cancer) is sufficiently unique to be able to identify an individual if paired with other available information.

If the identifiers are coded before use or disclosure for the research, the code may not be derived from any information about the patient or plan member. For example, the code may not be derived from the individual’s social security number, medical record number or name (such as initials), and may not be capable of being translated to identify the individual.

A covered entity may have one of its employees or a third party de-identify the PHI before use or disclosure of the information for research purposes. This process of de-identifying PHI is treated as covered entity “health care operations,” which may be done without the individual’s authorization.⁷⁷

When a non-employed third party (including a non-employed researcher) does the de-identification, the covered entity must have a business associate agreement in place with that third party.⁷⁸ The third party is a business associate of the covered entity for purposes of de-identifying the data, even if the de-identified is not used by the covered entity.⁷⁹ The definition of “health care operations” does not carry any requirement that the covered entity receive financial or any other benefit from the de-identified data.⁸⁰ However, after the de-identification process, the business associate may not retain the fully-identifiable information for research without following one of the other HIPAA rules for use or disclosure of PHI for research.⁸¹

The second de-identification method is that the covered entity can 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 covered entity must keep this documentation for six years. The OCR published an extensive guidance document on de-identification of PHI.⁸²

⁷⁷ *Id.* §§ 164.501 (defining health care operations), 164.506 (use or disclosure of PHI for health care operations).

⁷⁸ *Id.* §§ 164.502(e), 164.504(e); *see also* NIH, CLINICAL RESEARCH AND THE HIPAA PRIVACY RULE 14 (Feb. 2004) (NIH PUB. No. 04-5495) [hereinafter NIH, Pub. No. 04-5495], *available at* http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf (“The Privacy Rule considers [de-identification] to be a health care operation, as defined at section 164.501, of the covered entity. As such, a covered entity could contract with a business associate, including a researcher, to create de-identified data or a limited data set.”).

⁷⁹ 45 C.F.R. § 164.502(d)(1); *see also* NIH, PUB. No. 04-5495, at 14, *supra* (concluding that a covered entity may disclose its PHI to a third party researcher, for the researcher to de-identify that information to support the researcher’s research (not the covered entity’s research)).

⁸⁰ *See* 45 C.F.R. § 164.501 (defining “health care operations”).

⁸¹ *Id.* §§ 164.502(e), 164.504(e).

⁸² *See* OCR, GUIDANCE REGARDING METHODS FOR DE-IDENTIFICATION OF PROTECTED HEALTH INFORMATION IN ACCORDANCE WITH THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) PRIVACY RULE (Nov. 26, 2012), *available at* https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf.

(4) Limited Data Sets

A Limited Data Set is partially de-identified patient information. A Limited Data Set may not include any of the identifiers listed under the de-identification rule, except for: (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.⁸³ The research personnel who access, review, collect, or receive a Limited Data Set must sign a DUA, in which they agree to protect the confidentiality of the information. This requirement applies to internal personnel, as well to outside researchers.

A DUA must do 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 DUA 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 DUA 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 DUA;
 3. Report to the covered entity any use or disclosure of the information not provided for by its DUA 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 represented in the information.⁸⁴

A business associate agreement is not required when the covered entity discloses a Limited Data Set under a DUA.⁸⁵ However, a business associate agreement is required if the recipient is also the entity that will create the Limited Data Set.

⁸³ 45 C.F.R. § 164.514(e).

⁸⁴ *Id.* § 164.514(e)(4).

⁸⁵ *Id.* § 164.504(e)(3)(iv) (“A covered entity may comply with this paragraph and § 164.314(a)(1) if the covered entity discloses only a limited data set to a business associate for the business associate to carry out a health care operations function and the covered entity has a data use agreement with the business associate that complies with § 164.514(e)(4) and § 164.314(a)(1), if applicable.”); *see also* 78 Fed. Reg. at 5601 (“Response: We have prior guidance that clarifies that if only a limited dataset is released to a business associate for a health care operations purpose, then a data use agreement suffices and a business associate agreement is not necessary. To make this

(5) Activities to Prepare for Research

If researchers merely want to access or review PHI to prepare for research, researchers may view that information if they provide the covered entity with the following representations in writing:

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.

Activities to prepare for research include 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 to function as a site for a clinical trial.⁸⁶ Contacting patients to solicit participation in a clinical trial is not an activity to prepare for research.⁸⁷

If researchers will need to remove PHI from the covered entity's premises to review it, the researchers must ask the IRB to waive authorization instead, or another HIPAA option must be satisfied. In its guidance document entitled "Health Services Research and the HIPAA Privacy Rule," the OCR explained that while remote access alone is not necessarily a removal of PHI, the printing, copying, saving, or electronically faxing of such PHI would be considered to be a removal of PHI.⁸⁸

(6) Patient Recruitment

HIPAA permits the use or disclosure of PHI for patient recruitment.⁸⁹ First, a health care provider may contact the provider's own patients to determine if the patients are interested in participating in a clinical trial. If the provider or the provider's employees contact the provider's own patients, that use of PHI is for either "treatment" (if it is a research study that involves treatment) or "health care operations" purposes, both of which are permitted without patient authorization under HIPAA.⁹⁰ The health care provider also may use a non-employed third party (including the researcher) to contact patients for recruitment purposes, but the provider first would have to obtain a business associate

clear in the regulation itself, we are adding to Sec. 164.504(e)(3) a new paragraph (iv) that recognizes that a data use agreement may qualify as a business associate's satisfactory assurance that it will appropriately safeguard the covered entity's protected health information when the protected health information disclosed for a health care operations purpose is a limited data set. A similar provision is not necessary or appropriate for disclosures of limited data sets for research or public health purposes since such disclosures would not otherwise require business associate agreements.").

⁸⁶ See NIH, PUB. NO. 04-5495, at 5, *supra*.

⁸⁷ *Id.* at 4.

⁸⁸ NIH, HEALTH SERVICES RESEARCH AND THE HIPAA PRIVACY RULE 14 (May 2005) (NIH PUB. NO. 05-5308), available at <http://privacyruleandresearch.nih.gov/pdf/HealthServicesResearchHIPAAPrivacyRule.pdf>.

⁸⁹ NIH, PUB. NO. 04-5495, at 4, *supra*.

⁹⁰ 45 C.F.R. §§ 164.501 (definitions of "treatment" and "health care operations"), 164.506.

agreement with the third party.⁹¹ Finally, the researcher can request an IRB to partially waive authorization under Section III.B.2.a(2) above, so that authorization is not required for the initial contact, but will be sought for enrollment in the study. Contacting patients for recruitment is not a “preparatory to research” activity under Section III.B.2.a(5) above.⁹²

b. Minimum Necessary

HIPAA covered entities must observe the “minimum necessary standard” in releasing PHI for research purposes. A covered entity is entitled to rely on a request for PHI by another covered entity as being the minimum amount of PHI needed for the research.⁹³ Moreover, FDA-Catalyst policies require Collaborating Institutions’ requests for information to be limited to the minimum necessary to accomplish the intended purposes. Covered entities thus may rely on FDA-Catalyst research requests as being limited to the minimum amount of PHI necessary for the FDA-Catalyst activities.

Moreover, when uses or disclosures are made pursuant to an IRB waiver, the covered entity making the use or disclosure may rely on the IRB waiver as describing the minimum amount of information necessary for the use or disclosure. Likewise, when uses or disclosures are made pursuant to the preparatory-to-research rule, the covered entity may rely on the representations of the researcher as describing the minimum necessary.⁹⁴

⁹¹ *Id.* §§ 164.502(e), 164.504(e).

⁹² See NIH, PUB. NO. 04-5495, at 4, *supra* (“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.”).

⁹³ See 45 C.F.R. § 164.514(d)(3)(iii)(B) (“A covered entity may rely, if such reliance is reasonable under the circumstances, on a requested disclosure as the minimum necessary for the stated purpose when: . . . (B) The information is requested by another covered entity. . .”).

⁹⁴ See *id.* § 164.514(d)(3)(iii)(D) (“A covered entity may rely, if such reliance is reasonable under the circumstances, on a requested disclosure as the minimum necessary for the stated purpose when: . . . (D) Documentation or representations that comply with the applicable requirements of §164.512(i) have been provided by a person requesting the information for research purposes.”); 65 Fed. Reg. 82461, 82545 (Dec. 28, 2000) (“In making a minimum necessary determination regarding the use or disclosure of protected health information for research purposes, a covered entity may reasonably rely on documentation from an IRB or privacy board describing the protected health information needed for research and consistent with the requirements of § 164.512(i), . . . A covered entity may also reasonably rely on a representation made by the requestor that the information is necessary to prepare a research protocol or for research on decedents. The covered entity must ensure that the representation or documentation of IRB or privacy board approval it obtains from a researcher describes with sufficient specificity the protected health information necessary for the research.”); HHS, FAQ: MAY A COVERED ENTITY ACCEPT DOCUMENTATION OF AN EXTERNAL INSTITUTIONAL REVIEW BOARD’S (IRB) WAIVER OF AUTHORIZATION FOR PURPOSES OF REASONABLY RELYING ON THE REQUEST AS THE MINIMUM NECESSARY? (Dec. 19, 2002), <https://www.hhs.gov/hipaa/for-professionals/faq/217/is-documentation-from-old-irb-reliable-evidence/index.html> (last visited Sept. 20, 2017) (“May a covered entity accept documentation of an external Institutional Review Board’s (IRB) waiver of authorization for purposes of reasonably relying on the request as the minimum necessary? Answer: Yes. The HIPAA Privacy Rule explicitly permits a covered entity to reasonably rely on a researcher’s documentation of an

c. Sale of PHI

Collaborating Institutions, including Data Partners, will receive compensation for conducting FDA-Catalyst research activities. Such compensation is not “in exchange for” PHI, as explained above in Section III.B.1.e, and thus is not a “sale” of PHI. Moreover, the “sale” of PHI rule contains an exception permitting remuneration for disclosures for research, where the only remuneration received by the covered entity is a reasonable, cost-based fee to cover the cost to prepare and transmit the information.⁹⁵

C. COMMON RULE COMPLIANCE

1. Distinguishing Between Public Health Practice, Public Health Research, and Research

Public health agencies, like the FDA, carry out two types of public health activities: public health practice and public health research.⁹⁶ Moreover, the Sentinel Data may be used for research that is not public health research. It is important to distinguish among these three categories for HIPAA and Common Rule compliance.

a. Public Health Practice

Public health practice “includes epidemiological investigations, surveillance, programmatic evaluations, and clinical care for the population... Underlying many of these activities is ... the collection and analysis of identifiable health data by a public health authority for the purpose of protecting the health of a particular community, where the benefits and risks are primarily designed to accrue to the participating community.”⁹⁷ Public health practice includes conducting surveillance to detect signals of emerging

Institutional Review Board (IRB) or Privacy Board waiver of authorization pursuant to 45 CFR 164.512(i) that the information requested is the minimum necessary for the research purpose. See 45 CFR 164.514(d)(3)(iii). This is true regardless of whether the documentation is obtained from an external IRB or Privacy Board or from one that is associated with the covered entity.”)

⁹⁵ 45 C.F.R. § 164.502(a)(5)(ii)(2)(ii) (permitting remuneration for disclosure of PHI and Limited Data Sets for research purposes “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”).

⁹⁶ See, e.g., HODGE GOSTIN, COUNCIL OF STATE & TERRITORIAL EPIDEMIOLOGISTS, PUBLIC HEALTH PRACTICE VS. RESEARCH 7 (2004); Paul J. Amoroso & John P. Middelhaugh, *Research vs. Public Health Practice: When Does a Study Require IRB Review?*, 36 PREVENTIVE MED. 250, 250 (2003); Dixie E. Snider, Jr. & Donna F. Stroup, *Defining Research When It Comes to Public Health*, 112 PUB. HEALTH REPS. 29, 30 (1997); CTRS. FOR DISEASE CONTROL & PREVENTION, U.S. DEP’T OF HEALTH AND HUMAN SERVS., GUIDELINES FOR DEFINING PUBLIC HEALTH RESEARCH AND NON-RESEARCH 2 (1999), available at <http://www.cdc.gov/od/science/integrity/docs/defining-public-health-research-non-research-1999.pdf>.

⁹⁷ Yale Interdisciplinary Center for Bioethics, *IRB Case: Public health practice vs. research*, available at <http://bioethics.yale.edu/research/irb-case-studies/irb-case-public-health-practice-vs-research> (citing JAMES G. HODGE, JR. & LAWRENCE O. GOSTIN, COUNCIL OF STATE & TERRITORIAL EPIDEMIOLOGISTS, PUBLIC HEALTH PRACTICE VS. RESEARCH (2004)).

threats to public health and safety; and collecting confidential information to confirm risk signals and investigate their causes.⁹⁸

Under the pre-Amended Common Rule, public health practice—including medical product surveillance—is not subject to the Common Rule, and thus is not subject to its informed consent and IRB review requirements. In fact, in January 2010, OHRP determined that the pre-Amended Common Rule does not apply to activities that are included in the [FDA] Sentinel Initiative.”⁹⁹ (See **Exhibit 1.**)

The Amended Common Rule even more clearly classifies the traditional Sentinel public health practice activities a non-research, as there is now an express exemption for “public health surveillance” activities.¹⁰⁰ The Amended Common Rule definition of public health surveillance activities may not be fully coextensive with the broader concept of “public health practice,” which is still excluded from the Common Rule if it does not meet the definition of “research.” Nonetheless, the Amended Common Rule definition of “public health surveillance” activities clearly encompasses the Sentinel medical product safety surveillance and support for FDA’s review of product effectiveness.

b. Public Health Research

Where public health practice applies existing know-how to improve the health of a specific population, public health research aims to develop new methodologies, techniques, and knowledge to improve public health practice in the future.

The Common Rule, like HIPAA, defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”¹⁰¹ Public health research is a subset of research. The distinguishing features of public health research are that (i) its primary aim is to improve public health practice in the future (as opposed to adding to general

⁹⁸ See Amoroso & Middaugh, *Research vs. Public Health Practice: When Does a Study Require IRB Review*, 36 PREVENTIVE MED. 250 (2003).

⁹⁹ On January 19, 2010, Jerry Menikoff, Director of the OHRP, wrote a letter to Rachel Behrman, then Acting Associate Director of Medical Policy, Center for Drug Evaluation and Research at the FDA, explaining that OHRP “has determined that the regulations this office administers (45 CFR part 46) do not apply to the activities that are included in the [FDA] Sentinel Initiative.” (See Exhibit 1.) Dr. Behrman then wrote on April 2, 2010, to Dr. Richard Platt at Harvard Pilgrim Health Care (the SOC), providing Dr. Menikoff’s letter and concluding that the OHRP’s “assessment applies to the work being conducted by [the SOC] and its subcontractors under contract number HHSF2232009100061, as the purpose of this contract is to carry out Sentinel Initiative activities that are included in the [FDA] Sentinel Initiative.” (See Exhibit 2.) Thus, disclosure of information for Sentinel System activities is not “research” that is subject to the Common Rule. This means that data sources providing information for Sentinel System medical product surveillance activities are not required by federal regulation to obtain approval of their IRBs for participation in the Sentinel System, and are not required to obtain a determination from their IRBs that these activities are “exempt.”

¹⁰⁰ 82 Fed. Reg. 7149, 7261 (Jan. 19, 2017) (noting, with respect to § __.102(l)(2), that the excluded public health surveillance activities are “limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from consumer products).”).

¹⁰¹ 45 C.F.R. § 46.102(d); 45 C.F.R. § 164.501.

scientific knowledge or improving clinical health care more generally),¹⁰² and (ii) it is generally performed by, or for, a public health agency and is often funded by a public health agency itself, although results may be published for wider general use.¹⁰³

Because the focus of both public health practice and public health research is on population-oriented efforts (as opposed to patient-specific measures),¹⁰⁴ the distinction between public health practice and public health research is often a thin one. Moreover, the broad definition of “research” leads some to treat a public health activity as research if it produces any generalizable knowledge, even incidentally.

Some organizations ask their IRBs to review whether an activity is public health practice *versus* public health research, although the regulations do not require that an IRB make this determination. Unfortunately, different IRBs and institutions apply different frameworks and reach different conclusions, at times leading to inconsistent classification of similar activities.

In response, scholars and public health agencies have proposed various frameworks to help IRBs distinguish public health practice from public health research/research. These frameworks take into account factors such as what is the primary intent of the activity; whether there is general or specific legal authority to conduct the activity; whether benefits of the activity flow mainly to the participating community as opposed to external communities; whether study structure involves randomization or experimental interventions; whether results will be published; and other factors.¹⁰⁵

Finally, scholarly commentary has suggested that Section 905 of the FDAAA (which authorized the Sentinel System) may provide legal support for FDA to take a broad view of public health practice, including research authorized by the FDA that uses Sentinel Data.¹⁰⁶ FDAAA grants FDA specific legal

¹⁰² Indeed, the Centers for Disease Control and Prevention (“CDC”), describe the central purpose of public health research “is to develop or contribute to generalizable knowledge to improve public health practice.” See CDC, DISTINGUISHING PUBLIC HEALTH RESEARCH AND PUBLIC HEALTH NONRESEARCH 3 (Pub. No. CDC-SA-2010-02) (July 29, 2010), available at <https://www.cdc.gov/od/science/integrity/docs/cdc-policy-distinguishing-public-health-research-nonresearch.pdf>.

¹⁰³ Yale Interdisciplinary Center for Bioethics, *IRB Case: Public health practice vs. research*, available at <http://bioethics.yale.edu/research/irb-case-studies/irb-case-public-health-practice-vs-research>.

¹⁰⁴ Lawrence O. Gostin, PUBLIC HEALTH LAW 4 (2d ed. 2008) (explaining that public health practice and public health research both focus on population-oriented efforts (as opposed to patient-specific measures) “to ensure the conditions for people to be healthy (to identify, prevent, and ameliorate risks to health in the population).”).

¹⁰⁵ See, e.g., JAMES G. HODGE, JR. & LAWRENCE O. GOSTIN, COUNCIL OF STATE & TERRITORIAL EPIDEMIOLOGISTS, PUBLIC HEALTH PRACTICE VS. RESEARCH 7 (2004); Paul J. Amoroso & John P. Middaugh, *Research vs. Public Health Practice: When Does a Study Require IRB Review?*, 36 PREVENTIVE MED. 250, 250 (2003); Dixie E. Snider, Jr. & Donna F. Stroup, *Defining Research When It Comes to Public Health*, 112 PUB. HEALTH REPS. 29, 30 (1997); CTRS. FOR DISEASE CONTROL & PREVENTION, U.S. DEP’T OF HEALTH AND HUMAN SERVS., GUIDELINES FOR DEFINING PUBLIC HEALTH RESEARCH AND NON-RESEARCH 2 (1999), available at <http://www.cdc.gov/od/science/integrity/docs/defining-public-health-research-non-research-1999.pdf>.

¹⁰⁶ See DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE MINI-SENTINEL DISTRIBUTED DATABASE (Mini-Sentinel Operations Center and Clinical Trials Transformation Initiative, 2014) 36-40, available at <https://www.sentinelinitiative.org/sentinel/methods/developing-approaches-conducting-randomized-trials-using->

authority to use Sentinel Data for a broad array of advanced drug safety studies (including certain studies related to effectiveness), and FDA’s legal duty to see that these studies are conducted “support a finding that the studies are public health practice.”¹⁰⁷

Even though FDAAA may provide legal support for a broad view of public health practice, FDA has decided to take a conservative approach and will treat all of the currently proposed FDA-Catalyst activities as non-public health (general biomedical) “research” and obtain IRB review for those activities. In part, this reflects FDA’s understanding of the complexities that IRBs and HIPAA-covered entities face as they navigate the at-times conflicting (and now, changing) regulatory landscape of HIPAA and the Common Rule. Until the public health practice/public health research distinction is resolved with more clarity, the FDA will avoid doubt by obtaining IRB review of the proposed FDA-Catalyst activities.

c. General Non-Public Health Research

The final category is research that is not “public health research,” because the primary aim is not to improve public health practice in the future. Rather, the primary aim is to improve general scientific knowledge or clinical health care more generally. The Common Rule treats public health research the same as any other non-public health research.

Table 2 compares how the HIPAA Privacy Rule and the pre-Amended and Amended Common Rules define and address public health practice, public health research, and non-public health research.

[mini-sentinel-distributed](#); see also Barbara J. Evans, *Congress’ New Infrastructural Model of Medical Privacy*, 84 NOTRE DAME LAW REVIEW 585, 617 (2009).

¹⁰⁷ Evans, 84 NOTRE DAME LAW REVIEW at 617, *supra*.

Table 2. How Public Health Practice, Public Health Research, and Research Are Addressed under the HIPAA Privacy Rule, the Pre-Amended Common Rule, and the Amended Common Rule (repeat of Table 1).

	HIPAA Privacy Rule	Pre-Amended Common Rule	Amended Common Rule
<p>Public Health Practice</p> <p><i>The application of existing knowledge and techniques to protect the public's health.</i></p>	<p>The Privacy Rule does not require individual authorization to disclose PHI to a public health authority for public health activities.</p>	<p>The pre-Amended Common Rule does not define public health practice. Public health agencies and IRBs must infer whether an activity is public health practice by determining that it does not fit into the Common Rule's definition of human subject research.</p>	<p>The Amended Common Rule clarifies that "public health surveillance activities" are not subject to the Common Rule. There is another new exemption where the use of the data will be regulated by HIPAA as public health activity, research, or health care operations.</p>
<p>Public Health Research</p> <p><i>Studies performed by or for a public health authority to create new generalizable knowledge to improve public health practice in the future.</i></p>	<p>The HIPAA Privacy Rule does not require individual authorization to disclosure PHI to a public health authority for public health activities. While "public health research" is not defined, it arguably is included in "public health activities."</p>	<p>The pre-Amended Common Rule does not recognize a distinction between public health research and other research. When a public health activity fits within the Common Rule's definition of research, the activity is considered research.</p>	<p>The Amended Common Rule does not recognize a distinction between public health research and other research. All public health research is subject to the Common Rule (unless the transfer of data is to an entity regulated by HIPAA).</p>
<p>General Research</p> <p><i>Research that is not classified as "public health research."</i></p>	<p>The HIPAA Privacy Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Disclosures of data for non-public health research are not eligible for the HIPAA exemption for disclosures of PHI to a public health authority for public health activities.</p>	<p>The pre-Amended Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.</p>	<p>The Amended Common Rule adopts the same basic definition of human subject research as the pre-Amended Common Rule, but narrows the definition by expressly excluding four activities that are declared not to be research</p>

2. The Common Rule Application to FDA-Catalyst Research

This Section discusses the Common Rule requirements for the conduct of human subjects research. The pre-Amended Common Rule defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”¹⁰⁸ The Amended Common Rule adopts the same basic definition of human subject research as the pre-Amended Common Rule, but narrows the definition by expressly excluding four activities that are declared not to be research (including medical product surveillance activities).¹⁰⁹

a. Informed Consent

If informed consent is required under the Common Rule, the informed consent document must discuss how the participant’s information will be treated confidentially in the study. While the rule does not have specific requirements, it is common practice to include a description of what categories of individuals will have access to what information through the study.¹¹⁰ In addition, the Common Rule requires an informed consent document to discuss any reasonably foreseeable risks to participating in research.¹¹¹ If Data Partners include genetic information in the Common Data Model, such as results of genetic testing, the Genetic Information Nondiscrimination Act (“GINA”)¹¹² is relevant to the discussion of those risks. The OHRP and has published guidance on IRB approval of genetic research and appropriate content for informed consent documents.¹¹³

When the amendments to the Common Rule take effect, informed consent documents will need to be restructured and will have additional information relating to privacy and confidentiality. The amendments place an emphasis on the understandability of informed consent documents: they require key information to be stated at the top of the document, and require the document as a whole to provide sufficient detail and be presented in a way that facilitates the participant’s understanding of the reasons to participate in the study or not.¹¹⁴ Moreover, if the research will involve the collection of identifiable information, the informed consent will need to describe whether de-identified information might be used for future research. Specifically, one of the following statements will need to be included:

¹⁰⁸ 45 C.F.R. § 46.102(d).

¹⁰⁹ 82 Fed. Reg. at 7260-61 (Amended Common Rule at § __. 102(l)).

¹¹⁰ 45 C.F.R. § 46.116(a)(5) (requiring “a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained”).

¹¹¹ *Id.* § 46.116(a)(2).

¹¹² Public Law 110-233, 122 Stat. 881 (2008), *codified at* 42 U.S.C. § 2000ff note. For additional details regarding the provisions of GINA, see HHS, GINA: THE GENETIC INFORMATION NONDISCRIMINATION ACT OF 2008: INFORMATION FOR RESEARCHERS AND HEALTH CARE PROFESSIONALS (Apr. 6, 2009), *available at* <http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf>.

¹¹² Pub. L. 110-223, 122 Stat. 905 (2008) (*codified at* 42 U.S.C. § 2000ff, *et seq.*).

¹¹³ See OHRP, GUIDANCE ON THE GENETIC INFORMATION NONDISCRIMINATION ACT: IMPLICATIONS FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS (Mar. 24, 2009), *available at* <https://www.hhs.gov/ohrp/regulations-and-policy/guidance-on-genetic-information-nondiscrimination-act/index.html>.

¹¹⁴ 82 Fed. Reg. at 7265-66 (Amended Common Rule at § __.116(a)(5)).

(1) that the identifiers might be removed, and that the resulting de-identified information may be used or disclosed to another investigator for future research studies without additional consent, or (2) that the information will not be used or disclosed for future research studies, even if identifiers are removed.¹¹⁵ The consent also will be required to state whether clinically relevant research results, including individual research results, will be disclosed to participants, and if so, under what conditions.¹¹⁶ There also are a variety of other new provisions related to biospecimens,¹¹⁷ but those provisions are not relevant to FDA-Catalyst research.

Perhaps the most significant change in the Common Rule amendments is the concept of “broad consent,” which researchers may use (in place of a full informed consent or IRB waiver of informed consent) if they are requesting consent for the storage, maintenance or use of identifiable information for secondary research (where the information was collected for non-research purposes or for purposes other than the proposed research).¹¹⁸ (The broad consent rules similarly apply to biospecimens.) Broad consent is required to include a number of elements, such as a description of the types of research that may be conducted in the future and by whom, and what type of information will be used, along with other elements described in the footnote.¹¹⁹ Under the new rules, the storage or maintenance of

¹¹⁵ *Id.* at 7266 (Amended Common Rule at § ___.116(b)(9)).

¹¹⁶ *Id.* (Amended Common Rule at § ___.116(c)(8)).

¹¹⁷ *Id.* (Amended Common Rule at § ___.116(c)(7) (if the research participant’s biospecimens may be used for commercial profit (even if they are de-identified), the informed consent will be required to state that, and whether the participant will share in the commercial profit); *id.* (Amended Common Rule at § ___.116(c)(9)) (if the research will involve biospecimens, the informed consent will be required to state whether the research will or might include whole-genome sequencing).

¹¹⁸ *Id.* at 7266-67 (Amended Common Rule at § ___.116(d)).

¹¹⁹ Specifically, “broad consent” requires:

- “(1) The information required in paragraphs (b)(2), (b)(3), (b)(5), and (b)(8) and, when appropriate, (c)(7) and (9) of this section;
- (2) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- (3) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- (4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- (5) Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject’s identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
- (6) Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

identifiable private information for potential secondary research is exempt from the Common Rule if an IRB conducts a limited IRB review and makes the determination that broad consent will be obtained and documented, and that there are provisions to protect privacy and confidentiality in the event of a change in the way the information is stored.¹²⁰ Secondary research may then be conducted with the stored information if broad consent was obtained and documented, an IRB conducts a limited IRB review and makes the determination that the research is within the scope of the broad consent, and the researchers will not return individual research results to individuals.¹²¹ If broad consent is sought but refused by an individual, the IRB cannot later waive the consent requirement for that individual.¹²²

b. Waiver of Informed Consent

If it is not feasible to get research participants' informed consent, researchers may ask an IRB to waive the Common Rule informed consent requirement. 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 of consent 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.¹²³

When the amendments to the Common Rule are effective, they will add one more criterion for waiver of informed consent. In addition to the four existing criteria, the IRB will be required to find that, if the research involves using identifiable information, the research could not practicably be carried out

(7) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm." *Id.*

¹²⁰ *Id.* at 7261-62 (Amended Common Rule at § ___.104(d)(7)) (criteria for exemption); *id.* at 7264 (Post-2018 Common Rule at § ___.111(a)(8) (limited IRB review).

¹²¹ *Id.* at 7261-63 (Amended Common Rule at § ___.104(d)(8)) (criteria for broad consent exemption). Specifically: "(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and

(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results." *Id.*

¹²² *Id.* at 7265-67 (Amended Common Rule at § ___.116(f)(1)).

¹²³ 45 C.F.R. § 46.116(d); *id.* § 46.101(i); 61 Fed. Reg. 51531 (Oct. 2, 1996) (waiver of informed consent in emergency research).

without using the information in an identifiable format.¹²⁴ This criterion was modeled on the comparable element for waiver under HIPAA.¹²⁵ Additionally, if alteration of consent is sought, the rule will not allow certain core elements of the consent to be changed or omitted.¹²⁶

The revised Common Rule also will prohibit waiver of informed consent for individuals who previously were asked to sign a “broad consent” to store or use the information for future research, but declined to sign.¹²⁷ Thus, if a Data Partner is using PHI it obtains through a broad consent, the Data Partner would need to confirm that none of the individuals included previously declined to sign a broad consent concerning the information collected, before using or disclosing information pursuant to an IRB waiver of informed consent.

c. De-Identified Data

The treatment of de-identified information under the Common Rule is somewhat different than its treatment under HIPAA. As explained above, an entity does not conduct “human subject research” under the HHS regulations if the information was not collected for currently proposed research and the investigator cannot readily ascertain the identity of the participants.¹²⁸ To de-identify information under the Common Rule, only identifiers that enable an investigator to readily ascertain the identity of a participant must be removed. For example, because a Limited Data Set does not contain any direct identifiers, a Limited Data Set will be treated as non-identifiable information under the Common Rule, unless there is something in the data set that would enable an investigator to readily ascertain the identity of the participants.

Moreover, coding under the Common Rule follows different rules. The OHRP has clarified that, in order to ensure that an investigator cannot determine the identity of the participants in coded information: (1) 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 participants are deceased; (2) 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 (3) other legal requirements prohibit the release of the key to the investigators, until the participants are deceased.¹²⁹

The revised Common Rule will not change the criteria for de-identification,¹³⁰ except that the rule will introduce a new process through which federal departments and agencies implementing the Common Rule must reexamine the meaning of “identifiable” information periodically, including whether any

¹²⁴ 82 Fed. Reg. at 7265-67 (Amended Common Rule at § ____.116(f)(3)(iii)).

¹²⁵ *Id.* at 7224.

¹²⁶ *Id.* at 7226, 7265-67 (Amended Common Rule at § ____.116(f)(2)).

¹²⁷ *Id.* at 7265-67 (Amended Common Rule at § ____.116(f)(1)).

¹²⁸ 45 C.F.R. § 46.102(f); *see also* OHRP, GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS (Oct. 2008), available at <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/>.

¹²⁹ OHRP, GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS, *supra*.

¹³⁰ 82 Fed. Reg. at 7168-69.

technologies render information identifiable, such as whole-genome sequencing.¹³¹ Based on these evaluations, the departments and agencies may alter their interpretations of what is considered identifiable, and must publish in the Federal Register and maintain on HHS' website a list of technologies that produce identifiable information after notice and an opportunity for public comment.¹³²

d. Activities to Prepare for Research

Even if the Privacy Rule does not require individual authorization or IRB waiver of authorization for "preparatory to research" activities, the pre-Amended Common Rule requires IRB waiver of informed consent for a researcher to review the records of living individuals and to identify potential research participants.¹³³

Once the revised Common Rule takes effect, however, the Amended Common Rule will, like HIPAA, permit activities to prepare for research without individual consent or an express waiver of consent, but will still require IRB approval for these activities. The amendments to the Common Rule introduced a new provision that permits an IRB to approve a research proposal in which a researcher will obtain identifiable information by accessing records for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without informed consent.¹³⁴

e. Recruitment

Under the Common Rule, patient recruitment is "human subject research" that is governed by the federal regulations and requires IRB review.¹³⁵ Thus, even if the patient recruitment activities do not require IRB approval under the HIPAA Privacy Rule, access to information about potential human participants and contacting those prospective participants is "human subject research" that requires such review.

Once the revised Common Rule takes effect, however, the Amended Common Rule will, like HIPAA, permit patient recruitment activities without individual consent or express waiver of consent, but will require IRB approval for these activities. As explained in Section III.C.2.d above, the amendments to the Common Rule introduced a new provision that permits an IRB to approve a research proposal in which a researcher will obtain identifiable information by accessing records, or obtaining information through oral or written communication with the patient, for the purpose of recruiting prospective subjects without informed consent.¹³⁶

¹³¹ *Id.* at 7260 (Amended Common Rule at § ___.102(e)(7)).

¹³² *Id.*

¹³³ See 45 C.F.R. § 46.102(d), (f) (defining "research" on "human participants" as including examination of private information); *id.* § 46.109(a) (requiring IRB approval of research on human participants); *id.* § 46.116(c) (IRB approval of consent procedure to waive informed consent).

¹³⁴ 82 Fed. Reg. at 7265-67 (Amended Common Rule at § ___.116(g)). As part of its review of the entire research proposal, the IRB will have to determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, including for the preparatory-to-research activities. *Id.* at 7227.

¹³⁵ See 45 C.F.R. § 46.102(d), (f) (defining "research" and "human subject").

¹³⁶ 82 Fed. Reg. at 7265-67 (Amended Common Rule at § ___.116(g)).

f. The New Common Rule Exemption for Use of Data Regulated by HIPAA

The Amended Common Rule provides an exemption for the use or disclosure of PHI that is regulated by HIPAA as research, public health, or health care operations.¹³⁷ The Preamble to the Amended Common Rule explained that the exemption carves these activities out of the Common Rule because the information is already adequately protected by HIPAA, so as to avoid duplicative regulatory burden.¹³⁸ That means that, as long as PHI stays within or is transferred to a HIPAA covered entity or a HIPAA business associate, it is exempt from Amended Common Rule regulation. Disclosure of PHI to an outside entity that is not regulated by HIPAA would not be subject to the new exemption.

Applied to FDA-Catalyst activities, for example, research uses of Sentinel Data conducted within Data Partner sites that are HIPAA covered entities will be exempt from the Amended Common Rule.¹³⁹ The subsequent disclosure of Sentinel Data to the SOC, the FDA, or other non-covered entities will not be eligible for this new HIPAA exemption, but will not be classified as “human subjects” research under the Common Rule if the Sentinel Data are stripped of all direct identifiers. Therefore, starting in July 2018—assuming the revised Common Rule goes into effect as planned and assuming the data flow in Sentinel continues as currently structured—the use of Sentinel Data for FDA-Catalyst activities will not be subject to regulation under the Common Rule. However, the clinical study components involving interactions with individuals will continue to be subject to the Common Rule, because the HIPAA exemption applies only to the secondary use of data, where data is not collected for the specific research activities.

¹³⁷ *Id.* at 7261-62 (Amended Common Rule at § ____ .104(d)(4)(iii)) (“Except as described in paragraph (a) of this section, the following categories of human subjects research are exempt from this policy: . . . (4) Secondary research. The research involves only information collection and analysis involving the investigator’s use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of ‘health care operations’ or ‘research’ as those terms are defined at 45 CFR 164.501 or for ‘public health activities and purposes’ as described under 45 CFR 164.512(b)”); *id.* at 7194.

¹³⁸ *Id.* at 7194 (“HIPAA also provides protections in the research context for the information that would be subject to this exemption (e.g., clinical records), such that additional Common Rule requirements for consent should be unnecessary in those contexts. Under HIPAA, these protections include, where appropriate, requirements to obtain the individual’s authorization for future, secondary research uses of protected health information, or waiver of that authorization by an IRB or HIPAA Privacy Board. This provision introduces a clearer distinction between when the Common Rule and the HIPAA Privacy Rule apply to research in order to avoid duplication of regulatory burden. We believe that the HIPAA protections are adequate for this type of research, and that it is unduly burdensome and confusing to require applying the protections of both HIPAA and an additional set of protections.”).

¹³⁹ The Preamble noted that this exemption may be used only by investigators who are part of HIPAA covered entities. *Id.* at 7192.

D. USE OF A CENTRAL IRB TO OVERSEE FDA-CATALYST ACTIVITIES

1. Federal Law Requires or Permits Use of a Central IRB

The FDA-Catalyst program intends to use a central IRB to approve all FDA-Catalyst research projects. Federal law permits use of a central IRB and will require it once recent policy and rule changes take effect.

a. HIPAA

The HIPAA Privacy Rule permits a covered entity to rely on an external IRB, and thus permits use of a central IRB.¹⁴⁰

b. Common Rule

The Common Rule permits use of a central IRB, as there is no requirement in the Common Rule to use an IRB operated by the institution conducting the research.¹⁴¹ Moreover, when the revisions to the Common Rule become effective, the Common Rule will require use of a central IRB for multi-site research, with certain exceptions.¹⁴² Specifically, the Amended Common Rule will require any institution engaged in “cooperative research,” or research involving more than one institution, to rely upon approval by a single IRB for any part of the research conducted in the United States.¹⁴³ Institutions must comply with this requirement by January 20, 2020,¹⁴⁴ but may voluntarily use a single IRB to oversee cooperative research before that.¹⁴⁵ Further, to encourage institutions to feel comfortable relying on

¹⁴⁰ 45 C.F.R. § 164.512(i) (no requirement for local IRB to conduct review); *see also* OHRP and NIH, INSTITUTIONAL REVIEW BOARDS AND THE HIPAA PRIVACY RULE 2-3 (Aug. 15, 2003), *available at* https://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf (“The Privacy Rule does not impose any requirements for the location or sponsorship of an IRB convened for the purposes of acting on a request for approval of a waiver or an alteration of the Authorization requirement. Thus, an IRB approval for a waiver or an alteration of Authorization may be issued by an IRB that is unrelated to the institution conducting or sponsoring the specific research project, unrelated to the covered entity that creates or maintains the PHI to be used or disclosed for research, or different from the IRB with responsibility for monitoring the underlying research project. As a result, a waiver or an alteration of the Privacy Rule’s Authorization requirements could be obtained from a single IRB in connection with a multisite research activity or where the PHI necessary for the research will be used or disclosed by more than one covered entity.”).

¹⁴¹ 45 C.F.R. § 46.103 (no requirement for local IRB to conduct review); *see also* 82 Fed. Reg. at 7154 (noting that using a central IRB for multi-site research was voluntary before rule amendments).

¹⁴² *See* 82 Fed. Reg. at 7265 (Amended Common Rule at § ____ .114).

¹⁴³ *See id.* The only exceptions to the requirement to use a single IRB in cooperative research are for research for which more than single IRB review is required by law (including tribal law), or research for which a federal department or agency determines that use of a single IRB is not appropriate. *Id.* (Amended Common Rule at § ____ .114(b)(2)).

¹⁴⁴ *Id.* at 7259 (Amended Common Rule at § ____ .101(l)(2)).

¹⁴⁵ *Id.* at 7162.

IRBs they do not operate, the Common Rule was amended to permit agencies to enforce compliance directly against IRBs (rather than the institutions that relied on the IRB).¹⁴⁶

c. FDA Rules

The FDA also encourages the use of central IRBs. The FDA issued guidance in 2006 supporting the use of central IRBs for multi-site clinical trials for investigational new drug applications, especially where centralized review could improve efficiency of IRB review.¹⁴⁷ While the FDA statute used to require clinical trials involving medical devices to obtain review by local IRBs,¹⁴⁸ the recently-enacted 21st Century Cures Act eliminated that statutory requirement.¹⁴⁹

d. NIH Policy

Before the Common Rule was amended, and consistent with those rule changes, the NIH issued a policy requiring multi-site research protocols funded by the NIH to use a single IRB for all research sites in the United States.¹⁵⁰ The NIH policy was effective September 25, 2017.¹⁵¹

2. A Central IRB Does Not Require a Federalwide Assurance

An institution receiving funding from a federal department or agency for human subjects research must have a Federalwide Assurance (“FWA”) in place.¹⁵² Because research with FDA-Catalyst is federally-funded research, the Collaborating Institutions in the FDA-Catalyst project must have an FWA.

However, the reviewing IRB itself does not need an FWA (because that requirement applies to the institution conducting the research, not the IRB reviewing the research). However, an IRB reviewing

¹⁴⁶ *Id.* at 7259 (Amended Common Rule at § ____ .101(a), (1)(3)); *id.* at 7255 (“It is anticipated that institutions using an IRB that it does not operate [sic] will be reassured because compliance actions can be taken directly against the IRB responsible for the regulatory noncompliance, rather than the institutions that relied on that review. As a result of this change, we anticipate that FWA-holding institutions will increase their reliance on IRBs not operated by an FWA-holding institution when appropriate.”).

¹⁴⁷ See FDA, GUIDANCE FOR INDUSTRY: USING A CIRB REVIEW PROCESS IN MULTICENTER CLINICAL TRIALS 1 (Mar. 2006), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127013.pdf>.

¹⁴⁸ 21 U.S.C. 360j(g)(3)(A)(i) (requiring review by “local” IRB).

¹⁴⁹ 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033, § 3056 (2016) (striking references to “local” IRBs) (codified at 21 U.S.C. § 360j(g)(3)(A)(i), available at <http://docs.house.gov/billsthisweek/20161128/CPRT-114-HPRT-RU00-SAHR34.pdf>).

¹⁵⁰ See NIH, FINAL NIH POLICY ON THE USE OF A SINGLE INSTITUTIONAL REVIEW BOARD FOR MULTI-SITE RESEARCH, (JUNE 21, 2006) (NIH PUB. No. NOT-OD-16-094) [hereinafter “NIH POLICY”], available at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>. The only exceptions are where review by the proposed single IRB would be prohibited by a federal, tribal, or state law, regulation, or policy, or if there is a compelling justification for the exception.

¹⁵¹ *Id.*

¹⁵² 45 C.F.R. § 46.103. For terms of the FWA, see OHRP, FEDERALWIDE ASSURANCE (FWA) FOR THE PROTECTION OF HUMAN SUBJECTS, <https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subject/index.html> (last visited Oct. 31, 2017).

federally-supported research must be registered with the OHRP.¹⁵³ In addition, the institution conducting the research may need to designate the reviewing IRB in its FWA. If the institution has its own IRB (an “internal” IRB), it must designate the internal IRB in its FWA, but it does not need to list any external IRBs on which it relies.¹⁵⁴ If the institution does not have an internal IRB and relies on an external IRB, it is required to designate the IRB in its FWA only the external IRB on which it relies for the majority of its research, and must enter into a written IRB authorization agreement with all IRBs that review federally-funded research.¹⁵⁵ When the revised Common Rule is effective, institutions will no longer have to designate an IRB in their FWAs, although they still will be required to use IRBs that are registered with the OHRP.¹⁵⁶

¹⁵³ 45 C.F.R. §§ 46.103(b)(2), 46.501; OHRP, IRB REGISTRATION PROCESS FREQUENTLY ASKED QUESTIONS (FAQs), WHAT IRBS MUST BE REGISTERED, <https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/irb-registration/irb-registration-faq/index.html> (last visited Oct. 31, 2017) (“The HHS regulations at 45 CFR part 46, subpart E, require all IRBs to register with HHS if they will review humans subjects research conducted or supported by HHS and are to be designated under an assurance of compliance approved for federalwide use (i.e., an FWA) by OHRP.”).

¹⁵⁴ See OHRP, FEDERALWIDE ASSURANCE INSTRUCTIONS, STEP-BY-STEP INSTRUCTIONS FOR FILING A FEDERAL WIDE ASSURANCE, <https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/forms/fwa-instructions/index.html> (last visited Oct. 31, 2017) (“ITEM #6 - Designation of Institutional Review Board(s). This Institution assures that it will rely upon only Institutional Review Boards (IRBs) registered with OHRP to review the research to which this FWA applies. Designate all of your institution’s internal IRBs that review research under this FWA. If your institution has no internal IRBs, designate the external IRB that reviews all of the research to which this FWA applies or, if multiple external IRBs are relied upon, list the external IRB that reviews the largest percentage of research to which this FWA applies. Note: Institutions designating internal IRBs do not need to designate any of the external IRBs upon which it relies.”) (emphasis added); see also OHRP, IRB REGISTRATION PROCESS FREQUENTLY ASKED QUESTIONS (FAQs), *supra* (“Does a FWA have to be updated if an institution later relies on an IRB not included in the original FWA submission? Yes, if that IRB is an internal IRB, because all internal IRBs that review research covered by the institution’s FWA must be designated on that FWA. In addition, if the institution has no internal IRBs and has designated one external IRB, but decides to rely on a second external IRB that will review the largest percentage of research covered by its FWA, the institution must update its FWA to replace the first external IRB with the second IRB. Reliance on an external IRB, i.e. an IRB of another institution or organization, or an independent IRB, must be documented by a written agreement that is available for review by the OHRP upon request. OHRP’s sample IRB Authorization Agreement may be used for this purpose (see “Where can I find the instructions and forms for submitting?”) or the parties involved may develop their own agreement.”).

¹⁵⁵ See OHRP, IRBS AND ASSURANCES, <https://www.hhs.gov/ohrp/irbs-and-assurances.html> (last visited Oct. 31, 2017). For sample IRB Authorization Agreement language, see OHRP, INSTITUTIONAL REVIEW BOARD (IRB) AUTHORIZATION AGREEMENT, <https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/forms/irb-authorization-agreement/index.html> (last visited Oct. 31, 2017). The revised Common Rule will require institutions to document their reliance on IRBs; institutions already are required to do this under their FWAs, but the Common Rule adds a regulatory requirement to do so. This documentation can be done via agreement or policy. See 82 Fed. Reg. at 7181, 7261 (Amended Common Rule at § ____ .103(e)).

¹⁵⁶ See 82 Fed. Reg. at 7181, 7204-05 (“The final rule. . . adopts the NPRM proposal to delete the requirement in the pre-Amended Common Rule that institutions designate one or more IRBs on that institution’s FWA.”) Institutions still will need to ensure that the IRBs upon which they rely are registered with OHRP, and that the IRB’s makeup is appropriate for the research. See *id.* at 7181.

3. Benefits of Using a Central IRB

The support in federal rule and policy for using a central IRB for multi-site research reflects the growing consensus that a central IRB has many benefits. As the OHRP pointed out in the Preamble to the amendments to the Common Rule, review by a single IRB promotes efficiency and decreases administrative burdens to investigators and institutions, because it avoids the performance of duplicative reviews by multiple local IRBs.¹⁵⁷ For example, review by multiple IRBs of the research protocol adopted for the entire study often results in revisions that must be re-submitted to all of the reviewing IRBs, which can result in significant delays in the initiation of research projects and recruitment of subjects into studies.¹⁵⁸ The OHRP explained that “in many cases multiple IRB approvals increase burden and frequently delay the implementation of studies, increasing the costs of clinical trials and potentially stalling access to new therapies.”¹⁵⁹

Additionally, review by multiple IRBs can lead to inconsistencies in research protocol and informed consent documents, which can introduce variances in how the research is conducted, and in the make-up of the participants who enroll in the study across sites.¹⁶⁰ Commenters to the NIH’s draft policy noted that multiple IRB reviews “may actually contribute to some researchers’ reluctance to participate in rigorous, multi-site research and may incentivize smaller and simpler study designs.”¹⁶¹ Use of a central IRB reduces the risk of inconsistencies in the conduct of the research across sites.

Other potential benefits of using a central IRB include improved communication and oversight for research conducted across institutions. For example, when multiple IRBs review a study, a local IRB may identify a serious concern with a research protocol and may prevent the study from being conducted at its institution, but will not attempt to change the research protocol study-wide. Moreover, local IRBs may not convey those concerns to IRBs at other study sites; they are not required to do so, and may fear that they will breach their confidentiality agreements with sponsors by doing so. Additionally, local IRBs are able to make changes to the consent forms used at their sites, but do not communicate those changes to other IRBs. A central IRB is more likely to be informed of necessary changes to study documents and feel empowered to make those changes, resulting in greater protection of human subjects.¹⁶² In multi-site research, communication generally travels from sponsors to principal investigators to local IRBs; local IRBs generally do not communicate with each other. A central IRB offers a single forum for all participating organizations to communicate.

¹⁵⁷ *Id.*; see also NIH POLICY, *supra*.

¹⁵⁸ See 82 Fed. Reg. at 7208-09.

¹⁵⁹ *Id.* at 7209.

¹⁶⁰ See NIH POLICY, *supra* (“[Commenters] also indicated that review of the same protocol by multiple IRBs can sometimes lead to protocol and consent document changes that can introduce inconsistencies in the execution of the protocol across sites, lead to enrollment imbalances, and skew the analysis of the aggregated data.”); Jerry Menikoff, *The Paradoxical Problem with Multiple-IRB Review*, 363 NEW ENG. J. MED. 1591-93 (2010).

¹⁶¹ See NIH POLICY, *supra*.

¹⁶² See Jerry Menikoff, *The Paradoxical Problem with Multiple-IRB Review*, 363 NEW ENG. J. MED. 1591-93 (2010).

Finally, another advantage of central IRBs is the ability to employ full-time experts. In contrast to local IRBs, central IRBs often have access to a broad range of experts, and maintain the capacity to employ full-time personnel.¹⁶³

4. Use of IRB Authorization Agreements to Minimize Risks of Using a Central IRB

To minimize risks associated with using a central IRB, each FDA-Catalyst Collaborating Institution will enter into an IRB authorization agreement with the central IRB chosen to review FDA-Catalyst activities. An IRB authorization agreement delineates the roles and responsibilities of each party, so that all parties fully understand the allocation of obligations.¹⁶⁴ The agreement also will include a communication protocol to ensure that the central IRB will notify the institution directly of any significant issues that arise in the conduct of the research, such as adverse events, rather than relying on the principal investigator to notify the institution.

¹⁶³ Stephanie Pyle, *Benefits of Working with a Central IRB*, Vantage Point (2013), available at http://www.sairb.com/IRBForms/Benefits_of_Working_with_a_Central_IRB.pdf.

¹⁶⁴ Association for the Accreditation of Human Research Protection Programs, Inc., *Tip Sheet 24: Relying on An External IRB*, available at https://admin.share.aahrpp.org/Website%20Documents/Tip_Sheet_24_Relying_on_An_External_IRB.PDF.

IV. EXHIBITS

A. EXHIBIT 1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

JAN 19 2010

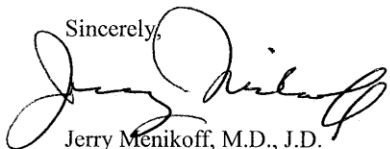
Rachel E. Behrman, M.D., M.P.H.
Acting Associate Director of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 22, Room 4208
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Dear Dr. Behrman:

The Office for Human Research Protections has determined that the regulations this office administers (45 CFR part 46) do not apply to the activities that are included in the Food and Drug Administration's Sentinel Initiative.

Do not hesitate to contact us if we can be of any further assistance.

Sincerely,



Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections

cc: Joanne Less, FDA

B. EXHIBIT 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

April 2, 2010

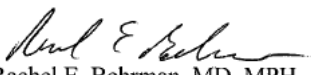
Dr. Richard Platt
Professor and Chair of the Department of Ambulatory Care and Prevention
Harvard Medical School and Harvard Pilgrim Health Care
133 Brookline Ave
Boston, MA 02215

Dear Dr. Platt:

The attached letter from the Office for Human Research Protections states: "The Office for Human Research Protections has determined that the regulations this office administers (45 CFR Part 46) do not apply to the activities that are included in the Food and Drug Administration's Sentinel Initiative."

This assessment applies to the work being conducted by you and your subcontractors under contract number HHSF2232009100061, as the purpose of this contract is to carry out activities that are included in the Food and Drug Administration's Sentinel Initiative.

Please let me know if you have any questions.


Rachel E. Behrman, MD, MPH
Sentinel Initiative, Executive Sponsor

C. EXHIBIT 3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

July 19, 2010

Dr. Richard Platt

Professor and Chair of the Department of Ambulatory Care and Prevention

Harvard Medical School and Harvard Pilgrim Health Care

133 Brookline Ave

Boston, MA 02215

Re: HIPAA Compliance for Data Sources Participating in the Mini-Sentinel Pilot Project

Dear Dr. Platt:

This letter affirms that the activities performed by the Mini-Sentinel Coordinating Center (MSCC) and its Collaborating Institutions,¹ in fulfillment of contract number HHS F2232009100061, are

¹ The Collaborating Institutions include:

1. America's Health Insurance Plans (AHIP)
2. Brigham and Women's Hospital Division of General Medicine
3. Brigham and Women's Hospital Division of Pharmacoepidemiology & Pharmacoeconomics
4. CIGNA Healthcare
5. Cincinnati Children's Hospital Medical Center
6. Columbia University Department of Statistics
7. Critical Path Institute (C-Path)
8. Duke University School of Medicine
9. HealthCore, Inc.
10. HMO Research Network including: Group Health Research Institute (GHRI) at the University of Washington (UW); Harvard Pilgrim Health Care Institute (HPHCI); Health Partners Research Foundation; Henry Ford Health Systems; Lovelace Clinic Foundation; Marshfield Clinic Research Foundation; Meyers Primary Care Institute (Fallon)
11. Humana-Miami Health Services Research Center (HSRC)
12. Kaiser Permanente Center for Safety and Effectiveness Research (CESR) including: Northern California (KPNC); Southern California (KPSC); Colorado (KPCO); Northwest (KPNW); Georgia (KPSE); Hawaii (KPHI); Ohio (KPOhio); MidAtlantic (KPMidAtlantic)
13. Outcome Sciences, Inc. (Outcome)
14. Risk Sciences International (RSI)
15. Rutgers University Institute for Health
16. University of Alabama at Birmingham (UAB)



public health activities for which HIPAA permits covered entities to disclose Protected Health Information (PHI) without individual authorization and without the need to obtain approval by or waiver of HIPAA authorization from an Institutional Review Board or Privacy Board.

The HIPAA Privacy Rule, at 45 C.F.R. § 164.512(b)(1)(i), permits covered entities to disclose PHI to a public health authority. The FDA is a public health authority, and has legal authority under Section 905 of the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) to conduct activities related to the project entitled, *Detection and Analysis of Adverse Events related to Regulated Products in Automated Healthcare Data. Efforts to Develop the Sentinel Initiative* (the Mini-Sentinel pilot project).

Under 45 C.F.R. § 164.501, a “public health authority” includes the FDA and “a person or entity acting under a grant of authority from or contract with” the FDA. Harvard Pilgrim Health Care is acting under the above-referenced contract with FDA to operate the MSCC. The Collaborating Institutions are under subcontract to Harvard Pilgrim Health Care to conduct activities in furtherance of FDA’s Mini-Sentinel pilot project. As such, MSCC and the Collaborating Institutions are all acting under a grant of authority from FDA and have the status of public health authorities under the HIPAA Privacy Rule for purposes of carrying out their responsibilities under the Mini-Sentinel pilot project.

HIPAA covered entities are required to verify that a person requesting PHI for public health purposes is a public health authority. For this purpose, HIPAA covered entities are entitled to rely on a written statement on appropriate government letterhead that the person is acting under the government’s authority (see 45 C.F.R. § 164.514(h)(2)(ii)(C)). This letter serves to provide the necessary written statement of authority to the MSCC and the Collaborating Institutions.

The HIPAA Privacy Rule also requires covered entities to comply with the minimum necessary rule at 45 C.F.R. § 164.502, but permits covered entities to rely on representations by a public health authority that it is requesting only the minimum amount of PHI necessary to carry out its public health mission (see 45 C.F.R. 164.514(d)(3)(iii)(A)). The Mini-Sentinel pilot project policies require MSCC and the Collaborating Institutions to request only the minimum necessary information that is required for purposes of carrying out their responsibilities. Thus, HIPAA covered entities may determine that requests from the MSCC and its Collaborating Institutions meet the minimum necessary standard.

Finally, because disclosures of PHI for the Mini-Sentinel pilot project are for public health activities, it is not necessary for HIPAA covered entities to obtain approval by their IRBs or

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- 17. University of Illinois at Chicago (UIC)
 - 18. University of Iowa, College of Public Health
 - 19. University of Pennsylvania School of Medicine
 - 20. Vanderbilt University School of Medicine
 - 21. Weill Cornell Medical College



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waiver of HIPAA authorization to provide data for Mini-Sentinel. The HHS Office for Human Research Protections (OHRP) has concluded that the regulations found in 45 CFR Part 46 (the "Common Rule") do not apply to activities related to the Sentinel Initiative and thus review by an IRB is not required by that rule.



Rachel E. Behrman, MD, MPH
Sentinel Initiative, Executive Sponsor