Response to the COVID-19 Pandemic: Contributions from the Medical Device Epidemiology Network

February 1, 2021

A White Paper

by the

Pandemic Response and Emergency Preparedness Task Force (PREPT)

Convened by

Medical Device Epidemiology Network (MDEpiNet)

I. Contents

II. Authors, Disclosure, Acknowledgements, and Dedication

Authors: Pandemic Response and Emergency Preparedness Task Force

Kristi Mitchell, MPH (co-chair)
Nick Tsinoremas, PhD (co-chair)
Andrew Auerbach, MD, MPH
Kevin M. Baskin, MD
Nancy A Dreyer, PhD, MPH, FISPE, Fellow DIA
Jeff Dunkel
Jens Eldrup-Jorgensen, MD, FACS
Laura Esserman, MD, MBA
Constantine Gatsonis, PhD
Marni Hall, PhD, MPH
Carolyn Hiller, MBA
Jack Lewin, MD
Dave Mandelkern, MS
Ross D. Martin, MD, MHA, FAMIA
Ali H. Mokdad, PhD
Elizabeth Paxton, PhD
Art Sedrakyan, MD, PhD
Vahan Simonyan, PhD
Julia Skapik, MD
James Tcheng, MD
William A Wood, MD, MPH

Disclosure: This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Acknowledgements: The authors would like to thank the federal employees who contributed to this report: Elise Berliner, PhD (AHRQ); Hartley LeRoy, MS (FDA); Kosta Makrodimitris, PhD (FDA); Danica Marinac-Dabic, MD, PhD, MMSc, FISPE (FDA); Gregory Pappas, MD, PhD (FDA); Murray Sheldon, MD (FDA); Scott Smith, PhD (OS/ASPE); Marta Steliac, MS (FDA); Meena Vythilingam, MD (OS/OASH).

Thanks also to Janice Tandler, MD for assisting with the preparation of this White Paper.

Dedication: This White Paper is dedicated to Michael Stephan Waters, our fallen COVID hero (1973-2020). Tribute Archive. Michael Stephan Waters Obituary-Rockville, Maryland, Sagel Bloomfield Value Choice | Tribute Archive. Available at: https://www.tributearchive.com/obituaries/18488618/Michael-Stephan-Waters. Accessed 4 December 2020.

III. Executive Summary

The COVID-19 pandemic has exposed many gaps in our ability to respond to national emergencies and the weaknesses of our national health information system. Early in the pandemic the Medical Device Epidemiology Network (MDEpiNet) responded to the emergency by creating the Pandemic Response and Emergency Preparedness Task Force (PREPT), which convened on July 20th, 2020. MDEpiNet is a global public private partnership that brings together leadership, expertise, and resources from health care professions, industry, patient groups, payers, academia, and government to advance a national system for patient-centered medical device evaluation and surveillance. In addition to leaders from MDEpiNet, PREPT includes representatives and leaders from regional Health Information Exchanges, the data systems of national community health centers, a large cancer research network, private sector systems aggregated databases and the American Society for Hematology Research Consortium. PREPT was tasked by MDEpiNet with producing this White Paper to identify the shortcomings of, and propose improvements to, the current health information system.

This White Paper focuses on solutions using real-world evidence (RWE) to respond to the pandemic and build the capacity of network real-world data (RWD) resources, called nodes. This network mirrors the fragmented health care delivery system of the US in which care (and RWD generation) is highly decentralized. Each node in the current real-world evidence (RWE) network employs its own unique infrastructure, methods, and tools and is evolving somewhat autonomously, being driven by emerging technology. Examples of nodes are national clinical society registries, public and private systems of claims data and EHR, data around person/patient-facing technology including apps and wearables, and vital records systems. MDEpiNet works to bring nodes together tactically around specific studies that have value to stakeholders. Studies are pursued that are useful to a sponsor of a study, for instance a medical product manufacturer; the study is then also used to promote development of methods, infrastructure, and interoperability to improve the system for future studies. This approach to building an RWE network can be described as “building the airplane as you fly it.”

Rarely does one data source provide answers to complex questions; RWD must be brought together from different nodes creating a wide network comprising data producers, data users, standards bodies, and emerging data collection technologies. MDEpiNet has created the Coordinated Registry Network (CRN) that links diverse data sources to provide evidence for a variety of purposes. This approach has been demonstrated as less costly and time-consuming compared to traditional studies. CRNs have become the building block of NEST (National Evaluation System for health Technology). One of the primary goals of the Task Force was to promote and develop the use of the CRN as a strategy to fight COVID-19 and future pandemics.

This White Paper comprises separate “planks” that identify specific gaps in the US response to the pandemic and offer relevant concept proposals. The planks can be read as standalone proposals and therefore repeat some conceptual aspects of the full report. As a set, the planks do not provide a linear blueprint for reform but instead specify interrelated goal-directed projects intended to align with national and global efforts.

Our approach is intended to both produce short-term results and foster long-term development, as the management of COVID-19 evolves with vaccines promising to change the course of the

pandemic. Most of the current public health measures (masks, social distancing, hygiene, and testing) continue to be needed now and for future pandemics. Under the Emergency Use Authorizations, vaccination of the population has begun with products about which little is known concerning long-term safety and efficacy. The national health information system envisioned in this White Paper would generate RWD for the post-market evaluation of newly introduced vaccines. For example, registries that collect data on vaccination could be linked to claims data to evaluate the efficacy and safety over time using strategies promoted in this White Paper. Finally, the White Paper promotes the creation of a national all payer claims database that would provide data on adverse events and of protection from infection with SARS-CoV-2 for new vaccines available through Emergency Use Authorizations and would advance the concept of CRNs, not only for COVID-19 but for most health care technology evaluations.

IV. Introduction and Background

The COVID-19 pandemic has exposed many gaps in our ability to respond to national emergencies and the weaknesses of our national health information system.[1,2] Early in the pandemic the Medical Device Epidemiology Network (MDEpiNet)[3] responded to the emergency by creating the Pandemic Response and Emergency Preparedness Task Force (PREPT). MDEpiNet is a global public private partnership that brings together leadership, expertise, and resources from health care professions, industry, patient groups, payers, academia, and government to advance a national system for patient-centered medical device evaluation and surveillance. In addition to representatives of the medical device ecosystem, PREPT includes leaders from a regional Health Information Exchange, the Chesapeake Regional Information System for our Patients (CRISP)[4]; the National Association of Community Health Centers (NACHC);[5] a large cancer research network, the I-SPY Trials;[6] a private sector company with aggregated databases, IQVIA;[7] and the American Society for Hematology Research Collaborative.[8] PREPT was tasked by MDEpiNet with producing this White Paper to identify gaps in the national response to COVID-19 and emergency preparedness related to health technology, and to propose solutions that MDEpiNet infrastructure can execute.

PREPT began work on July 20, 2020. Over a series of meetings, members brainstormed to identify gaps in our national response to the pandemic and potential solutions that the device ecosystem is uniquely suited to offer. Identification of gaps led to the forming of smaller work-groups that contributed to different sections of the White Paper, called "planks." Most of the planks take the form of gap analysis followed by relevant concept proposals. The concept proposals provide approaches to filling the gaps identified and ways for multiple stakeholders to come together to solve shared problems using real-world data (RWD). Finally, each plank discusses feasibility, grounding this report in an action agenda.

This White Paper comes at a time of great national effort to respond to the deadly pandemic.[9] Our proposals are offered here in full recognition that the US had an emergency preparedness pandemic plan in place that was highly regarded.[10] The Task Force is aware of many other recommendations that have been made and hopes that our perspective will find its place among others; we hope to create broader partnerships. We have tried to identify gaps in the current response to the pandemic and preparation for future pandemics that have not received much attention from others and

[1] Schneider EC. Failing the Test - The Tragic Data Gap Undermining the U.S. Pandemic Response. *N Engl J Med*. 2020 Jul 23;383(4):299-302. doi: 10.1056/NEJMp2014836. Epub 2020 May 15. PMID: 32412704.
[2] Keesara S, Jonas A, Schulman K. Covid-19 and Health Care's Digital Revolution. *N Engl J Med*. 2020 Jun 4;382(23):e82. doi: 10.1056/NEJMp2005835. Epub 2020 Apr 2. PMID: 32240581.
[3] MDEpiNet www.mdepinet.org Accessed December 10, 2020
[4] CRISP – Chesapeake Regional Information System For Our Patients. Available at: <https://crisphealth.org/. Accessed 4 December 2020.
[5] National Association of Community Health Centers https://www.nachc.org/ Accessed December 10, 2020
[6] The I-SPY Trials. Available at: <https://www.ispytrials.org/. Accessed 4 December 2020.
[7] IQVIA https://iqvia.org Accessed December 10, 2020
[8] American Society of Hematology Research Collaborative https://www.ashresearchcollaborative.org/s/ Accessed December 10, 2020
[9] McCulloch P, Sedrakyan A. COVID-19 has no effect on gravity. *BMJ Surgery, Interventions, & Health Technologies* 2020;**2:**e000046. doi: 10.1136/bmjsit-2020-000046
[10] Eissa N. Pandemic preparedness and public health expenditure. *Economies*. 2020;8(3):60.

provide responses that are feasible in the short term. Unfortunately, although many excellent existing sources of data exist and others have been created around COVID-19 mitigation, most of these sources are siloed and not interoperable. Addressing the poor performance of our national health information system will require major attention over many years, but the work must begin now.

Focus on Our Information Needs

MDEpiNet was founded to exploit the potential of real-world evidence (RWE) for evaluation of medical devices. Work to build national capacity to generate evidence using real-world data (RWD) was stimulated by law and policy around 21st Century Cures[11] and found its origin in the Institute of Medicine "Learning Health Care System" (LHCS) of over a decade ago.[12]

RWE, using data collected as part of routine clinical care, has been heralded as an answer to many of the woes of our medical system.[13] A wealth of untapped data — electronic medical records, medical imaging, mobile apps, and more recently low-cost gene sequencing and wearable devices, unlocked using artificial intelligence, cloud computing and blockchain — is proposed as the path to better diagnostics, personalized treatments, and early disease prevention for millions.[14] Comprehensive interoperability, a "plug and play" environment, that made possible international banking on cell phones, the "internet of things" and online shopping, could have tremendous benefit for medicine. Establishing such a health information system has been elusive, however, because clinical care tends to reside in data siloes, health IT systems are incompatible, and proprietary software makes health information difficult to exchange, analyze, and interpret.

Building on the vision of the LHCS, MDEpiNet's goal has been the creation of a network of nodes of RWD and other information resources to address the multiple evidence needs of stakeholders. The proposals in this White Paper promote the development of various nodes as high quality, interoperable data sources, and of networks that bring data together efficiently and rapidly, while preserving provenance. The nodes currently tend to be independent, without easy documentation of data provenance, and together do not constitute a functional network. RWD require extensive time and expense for curation to make them interoperable.[15] Data sharing in networks is constrained due to issues including confidentiality, privacy, and business concerns. These limitations decrease the utility of current data nodes and network[16] and reflect the fragmented health care delivery system of the US.

MDEpiNet's approach to building nodes and networks has been tactical, simultaneously producing value for a data user and building towards the future of a reusable network. RWE projects must

[11] Avorn, Jerry, and Aaron S. Kesselheim. "The 21st Century Cures Act--Will It Take Us Back in Time?." *The New England journal of medicine* 372.26 (2015): 2473-2475

[12] Institute of Medicine (US) Roundtable on Evidence-Based Medicine. The Learning Healthcare System: Workshop Summary. Olsen L, Aisner D, McGinnis JM, editors. Washington (DC): National Academies Press (US); 2007. PMID: 21452449.

[13] Sherman, Rachel E., et al. "Real-world evidence—what is it and what can it tell us." N Engl J Med 375.23 (2016): 2293-2297.

[14] Lehne, Moritz, et al. "Why digital medicine depends on interoperability." NPJ digital medicine 2.1 (2019): 1-5.

[15] Lohr S. For Big-Data Scientists, 'Janitor Work' Is Key Hurdle to Insights. The New York Times. https://www.nytimes.com/2014/08/18/technology/for-big-data-scientists-hurdle-to-insights-is-janitor-work.html. Published August 18, 2014. Accessed December 4, 2020.

[16] Beaulieu-Jones, Brett K., et al. "Examining the use of real-world evidence in the regulatory process." *Clinical Pharmacology & Therapeutics* 107.4 (2020): 843-852.

use existing data to address specific data needs and at the same time work to build the networks of the future by strategically developing tools, methods, and data sets.[17] A "build it and they will come" strategy was rejected for an "building the airplane as you fly it" approach. MDEpiNet studies are frequently paid for by industry in need of data to support regulatory submission. The studies funded by industry are not primarily motivated by the intent of building RWE, networks but nevertheless have enlarged the capacity for future studies.

As a public private partnership MDEpiNet brings together a consortium of stakeholders including industry, academic health care centers, patients, clinical specialty societies, and regulators to address specific data needs using RWD and build the RWE network. Over its ten-year history it has developed a strategy that leverages data collected by national specialty society registries and linked them to other resources (claims data, EHR, and mobile health technology data sources). The Coordinated Registry Network (CRN), first articulated in the Report of the Medical Device Registry Task Force, is a major strategy created by MDEpiNet to link the diverse data sources.[18] CRNs are some of the building blocks of the National Evaluation System for health Technology (NEST).[19]

CRNs can become a critical component of emergency preparedness and many of the proposals in this White Paper build on this approach to address the shortcomings of our present system. CRNs generate robust evidence more quickly than traditional studies and are less costly; also, CRNs are frequently a better source of data because they are larger, enabling us to look at populations in more detailed ways.[20,21] Clinical registries aggregate patient health data that are often organized around a single disease, condition, or procedure; the CRN expands the utility of those data. Alone, many of the RWD resources (registries, claims data, EHR) have limited value; linkage of these data sources by CRNs create utility by providing longitudinal information, enriched information about patients and outcomes, and better reflecting patients' experiences.[22, 23] Another major benefit of the CRNs is that once data is collected it can be used many times for a variety of purposes including regulatory decision making regarding safety and efficacy of medical products, quality assurance in health care systems, insurance coverage decisions, product development, and research.

The CRN is also a strategy to harmonize and link multiple registries to simultaneously study and compare multiple interventions. Data sets can be linked to follow cohorts longitudinally; e.g., CMS claims data, All Payers Claims Database and a vast array of new approaches to collecting and curating information collected as part of routine clinical care, e.g., apps, telehealth devices, EHR;

[17] Sedrakyan, Art, and Peter McCulloch. "Lighting a candle." (2019): e000008.
[18] Krucoff, M. W., et al. "Recommendations for a national medical device evaluation system." *Silver Spring (MD): Medical Device Registry Task Force and the Medical Devices Epidemiology Network* (2015).
[19] US Food and Drug Administration. "National Evaluation System for health Technology." (2017).
[20] Pappas, Gregory, et al. "Determining value of Coordinated Registry Networks (CRNs): a case of transcatheter valve therapies." *BMJ Surgery, Interventions, & Health Technologies* 1.1 (2019): e000003.
[21] Cronenwett, Jack L., et al. "Use of data from the Vascular Quality Initiative registry to support regulatory decisions yielded a high return on investment." *BMJ Surgery, Interventions, & Health Technologies* 2.1 (2020): e000039.
[22] Baird, C. E., et al. "Development of A Coordinated Registry Network for Women's Health Technologies." Value in Health 21 (2018): S179-S180.
[23] US Food and Drug Administration. "Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge Clinical Care and Research: A Report from the Medical Device Registry Task Force & the Medical Devices Epidemiology Network." (2015)

and patient/consumer-facing apps and wearables.[24] See Table 1 for a list of CRNs currently in use and under development.

Table 1. MDEpiNet CRNs

	CRN Name	Clinical Area
1.	Women's Health Technology Coordinated Registry Network (WHT-CRN)	Women's Health
2.	Vascular Implants Surveillance and Outcomes Network (VISION-CRN)	Vascular
3.	Cardiovascular Devices Coordinated Registry Network (CD-CRN)	Cardiac
4.	Orthopedic Devices Coordinated Registry Network (Ortho-CRN)	Orthopedic
5.	Abdominal Core CRN	Abdominal Hernia
6.	Devices Intended for Acute Ischemic Stroke Intervention (DAISI-CRN)	Acute ischemic stroke
7.	Venous Access National Guideline & Registry Development Coordinated Registry Network (VANGUARD-CRN)	Venous access
8.	Robotic Surgery Coordinated Registry Network (Robotic-CRN)	Robotic surgery
9.	Study of Prostate Ablation Evidence Development (SPARED-CRN)	Prostate ablation
10.	Temporomandibular Joint Coordinated Registry Network (TMJ-CRN)	Temporomandibular joint
11.	National Breast Implants Registry (NBIR)	Breast implants
12.	End-Stage Renal Disease Coordinated Registry Network (ESRD-CRN)	End-stage renal disease

[24] Atreja, A., et al. "Mobilizing mHealth innovation for real-world evidence generation." *Washington, DC: Duke-Margolis Center for Health Policy* (2017).

Themes and Principles of the Planks

The selection and production of the planks of this White Paper were directed by some shared themes and principles:

- Staying ahead of innovation

Responses to the pandemic must continually adjust to the introduction of new technology. Diagnostics, vaccines, treatment, and software solutions are rapidly being developed. Any response to the pandemic must accommodate these developments with a plan for infrastructure to evaluate and rapidly implement new measures as needed.

- Building on the national response: alignments and feasibility

PREPT worked to connect with major policy initiatives and programs responding to the pandemic. Rapid Acceleration of Diagnostics (RADx)[25] is the national HHS program that has provided important focus and funding for rapid scale up of testing and development of diagnostics for COVID-19. PREPT has aligned with RADx to ensure the feasibility of the proposals offered in the report of the Task Force. The White Paper also identifies places where other federal funding might be directed in the future. Policy initiatives addressed in this White Paper also build on a rich literature and existing initiatives to reform data collection and related issues, e.g., interoperability and need for an all payers claims database.[26,27,28] The Task Force weighs in on many existing policy initiatives and indicates avenues for expansion and further research.

The Task Force also focused on recommendations for short-term action, next steps. While the gap analyses presented here indicate that there is extensive work to be done in many areas, the concept proposals in the planks are the immediate steps to take in moving towards our goals.

- A focus on health disparities

Early in the pandemic it became clear that the burden of morbidity and mortality fell disproportionately on racial and ethnic minorities.[29] The social and economic conditions of other populations also lead to excess vulnerability to COVID-19.[30] The new AMA policy recognizes racism as a public health threat.[31] The response to the pandemic must incorporate the

[25] Rapid Acceleration of Diagnostics | RADx. National Institutes of Health. https://www.nih.gov/research-training/medical-research-initiatives/radx. Accessed December 4, 2020.

[26] Shachar C, Cohen G, Gerke S. Maximizing Use Of Claims Data To Address COVID-19: We Need To Revisit Gobeille v. Liberty Mutual: Health Affairs Blog. Health Affairs. https://www.healthaffairs.org/do/10.1377/hblog20200805.788636/full/. Published August 7, 2020. Accessed December 4, 2020.

[27] Young CL, Fiedler M. What can be done to improve all-payer claims databases? Brookings. https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2020/10/23/what-can-be-done-to-improve-all-payer-claims-databases/. Published October 26, 2020. Accessed December 4, 2020.

[28] Inventory and Prioritization of Measures To Support the Growing Effort in Transparency Using All-Payer Claims Databases. Ahrq.gov. https://www.ahrq.gov/data/apcd/backgroundrpt/intro.html#uses. Published 2020. Accessed December 5, 2020

[29] Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States [published online ahead of print, 2020 Jun 20]. *Clin Infect Dis*. 2020;ciaa815. doi:10.1093/cid/ciaa815

[30] Burström B, Tao W. Social determinants of health and inequalities in COVID-19. *Eur J Public Health*. 2020;30(4):617-618. doi:10.1093/eurpub/ckaa095

[31] American Medical Association. New AMA policy recognizes racism as a public health threat. Ama-assn.org. Accessed December 4, 2020. https://www.ama-assn.org/press-center/press-releases/new-ama-policy-recognizes-racism-public-health-threat

understanding of how racism and other social determinants of health lead to disparities and ensure that our proposals do not reproduce or reinforce these inequities. While none of the planks deals primarily with disparities, all of them address the fight to eliminate disparities as part of the solutions being recommended. Our health information system, a major focus of the planks, must be able to identify populations at risk and social determinants of health.

The Planks: Gap Analysis and Concept Proposals

The planks identify gaps in our national response to the COVID-19 and emergency preparedness as well as concrete proposals for work to address those gaps. These planks are intended to be used independently of this report, which accounts for the repetition and overlap that will be noted. The proposals emphasize feasibility, the next steps in what are transformational visions for our national capacity to collect and use RWD. The concept proposals' intent is to build interoperability, track data provenance, and facilitate sharing and linkage of data to build the nodes and network that will support the diverse evidence needs in health care. The work has two broad aims: supporting the response to the current pandemic and building an RWE infrastructure for future emergency preparedness. The various concept proposals are at different levels of development and feasibility because of the underlying nature of the gaps and barriers we face.

1. Testing and/or Vaccine Distribution Bubbles for Medically Vulnerable Patients

"Bubbles" are small groups of people who socialize only with each with the intention to prevent COVID-19 exposure. Social bubbles have sprung up spontaneously as a strategy to protect people from infection. Work is proposed to develop formal procedures to establish, maintain and evaluate bubbles for high-risk patients (e.g., those with multiple myeloma) who are followed in existing registries. Frequent use of point of service COVID-19 testing is proposed to be added to bubbles to increase their safety. Once the bubble members are vaccinated, the effectiveness of vaccination and continuation of the bubble can be evaluated.

2. Trial Design to Accommodate to a Rapidly Changing Pandemic

The rapidly changing patterns of a novel virus epidemic or pandemic outbreak over time and geography create difficulties in the design and execution of clinical trials for diagnostic tests, vaccines, and therapeutics. Methods for designing and implementing clinical trials that can rapidly adapt to these types of changes are currently lacking in the tool set of epidemiology. The plank proposes agile trials that use data from patients at disparate geographic locations and combine data from patients enrolled in different trials. Sharing control group patients across multiple trials would increase efficiency of this evaluation. A standing national capacity to rapidly evaluate treatments for emerging pathogens, including use of existing drugs that might be repurposed, is proposed. The proposed capacity requires logistical support and funding that can be rapidly deployed in the context of an emerging pathogen.

3. Real-world Evidence Solutions for Converting COVID-19 Diagnostics from EUAs to 510(k)

Diagnostic tests for COVID-19 are available under Emergency Use Authorization (EUA) that requires less evidence than the traditional clearance pathway, e.g., 510(k). Additional evidence of safety and efficacy of these diagnostics can be provided by RWD. A study is proposed to work with *in vitro* diagnostics companies and academic medical center data systems to develop evidence to further evaluate current testing. The FDA has provided direction for what may become a useful

strategy for data collection and post-market evaluation of diagnostics. The proposed pilot will explore how this pathway may be used.

4. The Federal Role in Building Real-world Evidence Infrastructure: Creating an "FCC for Health IT"

The underlying barrier to the use of RWD/RWE is the lack of interoperability (semantic, syntactic, and organizational). The Federal Communications Commission made possible huge global industries by providing standardization of data and processes for telecommunications. For health IT to progress, a similar federal function will be needed. The proposal calls for the creation of a national task force to envision such a new federal entity as a first step towards a major transformation. Until we address the fact that most RWD is too messy for use without extensive manual curation, we will make little progress towards better use of health data collected as part of routine care.

5. Creating a COVID-19 Module: Advancing the Evidence Base for Coordinated Registry Networks

CRN currently are functional in several specialty societies that are treating patients vulnerable to COVID-19 (e.g., dialysis patients being treated by vascular surgeons). A module to collect data on COVID-19 in medical specialty practices is proposed to be incorporated into their registries. A series of registries have been identified in a proposal to demonstrate the use of a COVID-19 module.

6. Remote Connected Care and Mobile Health in the COVID-19 Era: Solutions for Clinical Practice, RWE, and Trials

Telehealth has grown in importance, but like many aspects of health care, data collection is not well standardized. Aggregation and use of data for a national study to plan the response to emergencies is difficult. This concept proposal calls for work to develop these standards in a national public private partnership and evaluate them in a series of pilots.

7. Interoperability of Lab Data around COVID-19: Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD)

One of the major barriers for the use of RWD is the need for curation. Laboratory data is low-hanging fruit because it has been digitized and quality controlled with reference labs for decades. Despite the existence of coding systems, the lab data is nearly entirely lacking in interoperability because codes are nonstandardized and applied idiosyncratically at the lab and clinical level. Recently Congress required HHS to solve this problem for COVID-19 testing and turned to SHIELD to provide a harmonized coding system. The SHIELD solution can be extended to other laboratory data to decrease the time and expense of generating RWE.

8. Blockchain and Artificial Intelligence: Tools to Improve Efficacy of RWE Collection, Aggregation, and Analysis

Time and expense needed to secure, collect, aggregate, and analyze data are barriers to the use of RWE. Blockchain and artificial intelligence provide tools to improve efficiency. Pilots to implement new tools to be used with CRNs and examined with an evaluation framework are proposed.

9. PREPT Pandemic Coordinating Network (PCN): Uniting Islands of Expertise

The goal of this project is to demonstrate the feasibility and value of methodology for selection and aggregation of key data from available and emerging data silos to answer questions critical to progress toward a safe, evidence-based return to normal life. A pilot at the community level is proposed to bridge data between health and educational systems.

10. All Payers Claims Database: A Critical Resource for Real-World Evidence

A national All Payers Claims Database (APCD) can be a critical resource for RWE to evaluate new vaccines and medications for COVID-19. While registries provide a ready cohort of patients, longitudinal follow-up outcome data is expensive and time-consuming to create. Claims data have provided a ready source of longitudinal data when linked to registries for some robust outcomes. A national APCD to study the cost of medication has already been proposed in legislation; the same could be used to improve our RWE enterprise. A pilot to demonstrate the approach is proposed for a large state with existing APCD.

Update

The promise of vaccines is likely to change the course of the pandemic,[32] even while current public health measures (masks, social distancing, hygiene, and testing) continue to be needed. Under the Emergency Use Authorizations (EUA), the US will vaccinate with products about which little is known concerning long term safety and efficacy. The national health information system envisioned in this White Paper may provide a solution using RWE for evaluation of new vaccines available under EUA. Plank #10, "All Payers Claims Database: A Critical Resource for Real-World Evidence Use" promotes the creation of a national APCD that would provide data on vaccination and outcomes, adverse events data and evidence of protection from infection with SARS-CoV-2. Linkage of a national all payers claims database to registries (e.g., of patients most vulnerable to COVID-19 such as those with multiple myeloma or end-stage renal disease) could readily support development of understanding of how these patients fare with vaccinations and other treatment. This CRN approach could provide a part of the critical response to the pandemic needed now. Epidemiological and biostatistics methods have been developed to evaluate vaccines using RWD (i.e., CMS data) that can guide analysis of the type of data set envisioned here.[33]

Since the work on this White Paper began the National Strategy for the COVID-19 Response and Pandemic Preparedness has been issued by the new administration.[34] The work presented in the White Paper is aligned with that strategy.

[32] Zimmer C, Thomas K. What we know about the CDC's COVID-19 vaccine plans. *The New York Time* https://www.nytimes.com/article/covid-vaccine-a-b.html. Published November 30, 2020. Accessed December 4, 2020.

[33] Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, Lu M, Pratt D, Chu S, Wernecke M, MaCurdy T, Forshee R. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017-2018. *J Infect Dis*. 2019 Sep 13;220(8):1255-1264. doi: 10.1093/infdis/jiy716. Erratum in: J Infect Dis. 2019 Jun 5;220(1):179. PMID: 30561688.

[34] Whitehouse.gov. https://www.whitehouse.gov/wp-content/uploads/2021/01/National-Strategy-for-the-COVID-19-Response-and-Pandemic-Preparedness.pdf. Published 2021. Accessed January 28, 2021.

V. Planks

Plank # 1. Testing and/or Vaccine Distribution Bubbles for Medically Vulnerable Patients

Gap Analysis

Some individuals with transmissible SARS-CoV-2 infection are asymptomatic, and others are pre-symptomatic but still capable of passing on the infection before symptoms develop. Further, the infection can be transmitted through the air, with prolonged person-to-person exposure within six feet conferring an increased risk for transmission. For these reasons, physical distancing (sometimes referred to as "social distancing," which may be a misnomer, as true social isolation has profound adverse health consequences of its own) has emerged as a major public health strategy to contain the spread of the disease. "Bubbles" or "pods" have spontaneously emerged as a way in which small social groups try to protect themselves from infection by agreeing to maintain appropriate infectious risk-mitigating behaviors in exchange for relative physical proximity. This relative physical proximity functions to decrease social isolation while addressing other basic life needs shared by members of the bubble (for example, members of a bubble may be part of a family or household). A scientific literature has emerged describing the bubble phenomenon and begun to evaluate its use.[35,36]

The identification of this issue and the work to improve care for the medically vulnerable may also address similar needs of other vulnerable populations for which bubbles may be useful. Bubbles are being proposed to address infection control in schools, workplaces, and institutional care settings.[37]

The concept of a bubble is highly relevant for medically vulnerable individuals during the pandemic for several reasons. First, medically vulnerable individuals are often already familiar with the general idea of bubbles and risk-mitigating behaviors. For instance, recent hematopoietic cell transplantation recipients are highly immune suppressed and voluntarily limit their outpatient exposures to select numbers of individuals, while maintaining strict precautions around potential infectious exposures. Second, medically vulnerable individuals are often reliant on the presence of others to reduce social isolation and to help meet their basic life needs. Third, when individuals in a bubble are oriented towards the health and welfare of vulnerable individuals at the center, group members may be primed to engage in behaviors that can maintain integrity of the bubble and/or other strategies to further decrease infectious risk. In the context of the current pandemic, this means that such bubbles may be highly motivated to engage in enhanced SARS-CoV-2 surveillance testing strategies. These may also be well-situated for uptake of safe and effective vaccines, once these are available. Against a backdrop of uncertain public trust in newly developed vaccines, bubbles oriented around medically vulnerable individuals may be especially suited to facilitate vaccine distribution. Vaccinating all bubble members further decreases the risk for medically vulnerable individuals within the bubbles; members are more highly engaged to receive vaccines than others in the general population, as they wish to protect their most vulnerable fellow

[35] Leng T, Whie C, Hilton J, et al. The effectiveness of social bubbles as part of a Covid-19 lockdown exit strategy, a modelling study. *MedRxiv*. Published online 2020:2020.06.05.20123448. doi:10.1101/2020.06.05.20123448

[36] Dix A. Impact of a small number of large bubbles on Covid-19 transmission within universities. Preprint *arXiv [physics.soc-ph]*. Published online 2020. http://arxiv.org/abs/2008.08147

[37] D'angelo, Daniela, et al. "Strategies to exiting the COVID-19 lockdown for workplace and school: A scoping review." Safety science (2020): 105067

members. If medically vulnerable individuals can be identified and followed, then the members of their bubbles can be identified and followed as well.

A definition for "vulnerable" adopted for this report is drawn from RADx-UP, the HHS program that is working to ramp up testing in the United States. The RADx-UP has designated populations medically and/or socially vulnerable to COVID-19.[38]

PREPT includes leadership from clinical specialty societies. American College of Cardiology (ACC), American Society of Hematology (ASH) Research Collaborative, and the Vascular Quality Initiative (VQI) and these societies or their affiliate organizations maintain registries that can further characterize, identify, and contact medically vulnerable individuals. Thus, PREPT can contribute an expanded definition of medical vulnerability to national infection containment strategies and can leverage their organizations and registries to implement interventions that reduce risk among these individuals. For example, the ASH Research Collaborative maintains a Data Hub that connects networks of care delivery sites oriented around specific disease areas, initially multiple myeloma and sickle cell disease. Expansion to other malignant and non-malignant disease areas is envisioned in the near future and could be accelerated if doing so would help to address infection containment strategies during the pandemic, as suggested below. For current and future disease areas, sites are linked to the Data Hub through direct EHR integration, and individuals whose data are contained within the Data Hub are identifiable at the site level. The ASH Research Collaborative COVID-19 Registry for Hematology, a separate project distinct from the Data Hub, has already demonstrated that individuals with underlying hematologic malignancies are at increased risk for severe COVID-19 infection and for mortality following COVID-19 infection, with mortality estimates ranging from 20-28%.[39,40] These estimates are similar across hematologic malignancies, including multiple myeloma, and thus individuals with underlying hematologic malignancies can be considered medically vulnerable. The data concur with other databases and registry projects that show increased risk for patients with underlying hematologic malignancies and other active cancers.[41,42,43,44] Individuals with hematologic malignancies and other cancers are often older, have underlying or treatment-induced comorbid

[38] Tromberg, Bruce J., et al. "Rapid scaling up of Covid-19 diagnostic testing in the United States—the NIH RADx initiative." *New England Journal of Medicine* 383.11 (2020): 1071-1077.

[39] William A. Wood, Donna S. Neuberg, J. Colton Thompson, Martin S. Tallman, Mikkael A. Sekeres, Laurie H. Sehn, Kenneth C. Anderson, Aaron D. Goldberg, Nathan A. Pennell, Charlotte M. Niemeyer, Emily Tucker, Kathleen Hewitt, Robert M. Plovnick, Lisa K. Hicks; Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. *Blood Adv* 2020; 4 (23): 5966–5975. doi: https://doi.org/10.1182/bloodadvances.2020003170

[40] American Society of Hematology (ASH) Research Collaborative. COVID-19 Registry. Ashresearchcollaborative.org. Accessed December 4, 2020. https://www.ashresearchcollaborative.org/s/covid-19-registry

[41] Kuderer NM, Choueiri TK, Shah DP, Shyr Y, et al. COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020 Jun 20;395(10241):1907-1918. doi: 10.1016/S0140-6736(20)31187-9. Epub 2020 May 28. Erratum in: Lancet. 2020 Sep 12;396(10253):758. PMID: 32473681; PMCID: PMC7255743.

[42] Passamonti F et. al ITA-HEMA-COV Investigators. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol*. 2020 Oct;7(10):e737-e745. doi: 10.1016/S2352-3026(20)30251-9. Epub 2020 Aug 13. PMID: 32798473; PMC.

[43] Chari A et. al Clinical Features Associated with COVID-19 Outcome in MM: First Results from International Myeloma Society Dataset. *Blood*. 2020 Nov 6:blood.2020008150. doi: 10.1182/blood.2020008150. Epub ahead of print. PMID: 33156904.

[44] Garassino MC et. al; TERAVOLT investigators. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol*. 2020 Jul;21(7):914-922. doi: 10.1016/S1470-2045(20)30314-4. Epub 2020 Jun

illness, may have underlying immune dysregulation, and undergo additional disease-directed immunosuppressive treatments. They may also be at increased risk for COVID-19 associated complications, such as venous thrombosis. Individuals with non-malignant hematologic conditions, such as sickle cell disease,[45,46] have also been demonstrated to have increased risk from COVID-19 infection. PREPT also includes members associated with platform clinical trials for individuals with breast cancer, as well as the Vascular Quality Initiative (VQI),[47] which maintains registries that include individuals with end-stage renal disease, in addition to other stakeholders representing similarly vulnerable populations. Additionally, representation from the National Association of Community Health Centers could facilitate the enlistment of community health centers to work to create testing bubbles for their highly vulnerable patients.

The major limitation of adding testing and/or vaccine distribution to bubbles has been cost and accessibility of testing, on the one hand, and pending availability of efficacy and safety data for vaccines, on the other. However, the current environment is now well suited for reconsideration of both of these strategies. New testing modalities and those emerging promise more accurate, point of care tests at a cost that can facilitate wide use. Vaccine efficacy and safety data are now becoming available. The research approach needed to implement and evaluate the creation of bubbles and appropriate testing and vaccine distribution strategies is outlined here. The remainder of this section will focus on research questions and methods that may help frame future funding opportunities and proposals responding to those opportunities.

Concept Proposal

Goal:

Establish and evaluate testing and/or vaccine distribution bubbles for patients vulnerable to COVID-19 morbidity and mortality

Objectives:

- Develop strategies and materials to create bubbles around individuals who are at risk.[48,49]
- Identify medically vulnerable patients and the existing bubbles within which these individuals currently reside. Prioritization of patients may be appropriate for addition of testing and/or vaccine distribution. In cases of patients that have highly effective social bubbles, less frequent testing may suffice. This may be a sub-hypothesis.
- Develop criteria for adding testing and/or vaccine distribution to existing social bubbles surrounding medically vulnerable individuals.
- Develop strategies and implementation materials to create testing and/or vaccine distribution bubbles, including the enhancement of current bubbles where these exist.

[45] Panepinto JA, Brandow A, Mucalo L, Yusuf F, Singh A, Taylor B, Woods K, Payne AB, Peacock G, Schieve LA. Coronavirus Disease among Persons with Sickle Cell Disease, United States, March 20-May 21, 2020. *Emerg Infect Dis*. 2020 Oct;26(10):2473-2476. doi: 10.3201/eid2610.202792. Epub 2020 Jul 8. PMID: 32639228; PMCID: PMC7510702.

[46] Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion (Secure) SCD Registry. Welcome to Secure-SCD. Covidsicklecell.org. Accessed December 4, 2020. https://covidsicklecell.org/

[47] Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI). Improving Vascular Care. Vqi.org. Published June 12, 2014. Accessed December 4, 2020. https://www.vqi.org/

[48] Smith JA, Winters W. How to Form a Pandemic Pod. Greater Good. https://greatergood.berkeley.edu/article/item/how_to_form_a_pandemic_pod. Accessed December 4, 2020. Accessed January 27, 2021

[49] Prior R. Creating a pandemic social bubble: A how to guide. *CNN*. https://www.cnn.com/2020/04/30/health/how-to-form-a-bubble-wellness/index.html. Published April 30, 2020. Accessed December 4, 2020.

- Develop a framework for evaluating the effectiveness of testing and/or vaccine distribution in bubbles.
- Create tools for monitoring and evaluating testing and/or vaccine distribution bubbles; these should be integrated within a virtual, centralized program.

Research projects around testing bubbles for vulnerable patients should consider development of cost models and funding strategies for testing and/or vaccines. Barriers and best practices regarding reimbursement should be addressed. Criteria for use of intensive testing and/or vaccines should include risk of the index patient, quality of the social bubble to which testing and vaccines are to be added, and feasibility of implementation of testing and/or vaccine distribution within existing bubbles. Built into all testing bubble efforts should be the flexibility to incorporate new testing modalities as they become available on the market, or when they can be implemented on an experimental basis.

***Measures of Success**:*

Measures of success and outcome measures for the proposed research include monitoring testing rates, infection rates, and morbidity and mortality. The research should also strive to include rapid uptake of surveillance testing and/or vaccine distribution among vulnerable individuals and members of their bubbles over time. Comparison of rates of infections among participants and a control group should be included along with measurement of morbidity and mortality of vulnerable patients and bubble members. Consideration should also be given to comparing the rates of infection and consequences of infection to the larger population, which would require leveraging additional data sources.

Methods:

Platform trials and enhanced clinical specialty society registries, including ones that are affiliated with Coordinated Registry Networks (CRN), [50] are well poised to propose and conduct the research proposed here. These groups can be used to identify and contact medically vulnerable patients and have in place data collection systems. Proposed partners that may find "testing bubbles" useful include: Quantum Leap Healthcare Collaborative, the sponsor of the I-SPY TRIALs (adaptive platform clinical trial programs), ASH Research Collaborative Data Hub, Vascular Quality Initiative, American College of Cardiology, National Association of Community Health Centers, and VANGUARD.

Tools must be developed to create, sustain, and monitor bubbles. Bubble members must be trained in the use of point of care diagnostics to maintain quality over time. The use of telehealth tools and mobile apps that allow healthcare providers and other personnel to review testing and vaccine uptake results and monitor the bubbles remotely should be explored. The research proposed here should build on the existing literature concerning the prevention of infection in the immunocompromised host.[51] Beyond specific prophylactic and pre-emptive strategies, this should

[50] MDEpiNet CRN See https://www.mdepinet.net/coordinated-registry-networks Accessed December 11, 2020

[51] Bacigalupo A, Metafuni E, Amato V, Marquez Algaba E, Pagano L. Reducing infectious complications after allogeneic stem cell transplant. *Expert Rev Hematol*. 2020 Nov 3:1-17. doi: 10.1080/17474086.2020.1831382. Epub ahead of print. PMID: 32996342

include ways in which immunocompromised individuals have been counseled to avoid infectious exposures, such as through social distancing and travel advice.[52,53,54]

Mobile apps may be deployed as a tool to support implementation of testing and/or vaccination bubbles and monitoring their activities. This would ideally be deployed as part of a telehealth effort, allowing patients to protect themselves and undergo testing from their homes. A centralized monitoring app would also support reporting of tests and vaccines for purposes of medical care and public health.

A framework for evaluating testing bubbles does not yet exist in the academic literature. Some lessons may be learned from other evaluation frameworks that address the need of medically at-risk populations. For example, there are strategies for assessing biochemical markers that correlate with the degree of immunological response to vaccines. The term "correlate of protection" has been applied to three different levels of biochemical correlates of immunity involving measurable parameters. Definitions of these different concepts of immune correlates have been developed for "correlate of risk," "level 1 surrogate of protection," and "level 2 surrogate of protection." This framework for assessing these three aspects of immune correlates in vaccine efficacy trials may be useful to begin work on evaluation of bubbles on the immunological level.[55]

Feasibility:

Current members of PREPT and related platform trials, clinical societies, and NACHC are poised to take up this work and have begun creating testing bubbles for their patients. This concept proposal may assist PREPT partners to prepare for future funding opportunities, whether through NIH (RADx-UP or similar) or as part of an evolving coordinated federal response to the pandemic.

A peer reviewed manuscript may also be prepared to promote the idea of “bubbles” as a tool to fight the COVID-19 pandemic. This proposed peer reviewed article may include a fully developed evaluation framework for testing and/or vaccination bubbles.

[52] Bialy, C., et al. "International travel in the immunocompromised patient: a cross-sectional survey of travel advice in 254 consecutive patients." *Internal Medicine Journal* 45.6 (2015): 618-623.
[53] Samaha R, Kattan J. Hematopoietic stem cell transplantation dilemma during the COVID-19 era. *Future Oncology*. 2020. doi:10.2217/fon-2020-0414
[54] Samaha R, Kattan J. Hematopoietic stem cell transplantation dilemma during the COVID-19 era. *Future Oncology*. 2020. doi:10.2217/fon-2020-0414
[55] Qin, Li, et al. "A framework for assessing immunological correlates of protection in vaccine trials." *The Journal of infectious diseases* 196.9 (2007): 1304-1312.

Plank # 2. Trial Design to Accommodate to a Rapidly Changing Pandemic

Gap Analysis

The rapidly changing patterns of a novel virus epidemic or pandemic outbreak over time and geography create difficulties in the design and execution of clinical trials for diagnostic tests, vaccines, and therapeutics. The disease comes and goes in waves and may disappear suddenly only to appear in another place. Virus "hot spots" move quickly from one geographic location to another and create disruptions to health care and research infrastructure due to the pandemic. With almost 4000 COVID-19 trials worldwide in varying stages of execution as of late November 2020,[56] enrolling enough patients in both active and control arms in order to complete trial studies has become an issue.[57,58] The toolset of epidemiology is currently deficient in methods for designing and implementing clinical trials that can rapidly adapt to these changes in disease behavior. This gap can be understood as a series of challenges to clinical trial design to accommodate a rapidly changing pandemic:

- Too many trials competing for the same patients. Based on the severity of a localized viral outbreak, multiple trials may be launched simultaneously, in effect competing for the same limited number of patients and putting additional strain on the supply of patients to power trial arms.
- Too few patients to power active arms of trials. As the virus waxes and wanes at a given clinical trial site, it becomes difficult to enroll enough patients to power an arm of a trial before the supply of patients disappears.
- Increased difficulty in reaching target patient populations. The ability to study hard-to-reach subsets of the population such as some racial and ethnic groups or subjects with certain COVID-19-related conditions has had mixed success.
- Duplication of control arms consumes too many study patients. Each trial typically needs its own control arm, requiring that a large percentage of the eligible patients not be in the active arm, increasing the difficulty of powering the trial arms and aggravating the already short supply of potential study subjects.

The missteps and missed opportunities around evaluation of existing drugs that might have been repurposed for treatment of COVID-19 also point to the need for a standing national capacity to rapidly mount adequately powered clinical trials for evaluation of multiple therapeutic agents simultaneously to combat future pandemics and emerging pathogens.[59]

This problem is not unique to COVID-19. Previous viral outbreaks have generated reports of difficulties bringing clinical trials to conclusion due to lack of patient enrollment, for example in

[56] Mikulic M. COVID-19 clinical trials worldwide by region November 30, 2020. Statista. https://www.statista.com/statistics/1106306/coronavirus-clinical-trials-worldwide/. Published November 30, 2020. Accessed December 4, 2020.

[57] Bauchner H, Fontanarosa PB. Randomized Clinical Trials and COVID-19: Managing Expectations. *JAMA*. 2020;323(22):2262-2263. doi:10.1001/jama.2020.8115

[58] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. *N Engl J Med*. 2020;382(21):1969-1973. doi:10.1056/nejmp2005630

[59] Sultana, Janet et al. "Challenges for Drug Repurposing in the COVID-19 Pandemic Era." *Frontiers in pharmacology* vol. 11 588654. 6 Nov. 2020, doi:10.3389/fphar.2020.588654 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7677570/ Accessed Jan. 1 2021

Ebola,[60] SARS,[61]and Zika.[62] Various approaches, both statistical and through electronic data capture, have been proposed to pool data from patients from disparate trials as well as from multi-site platform trials.[63,64,65,66,67] Several different approaches have been proposed for reducing the number of patients required for the control group, including using external data sources to create a "synthetic control" [68,69] using Bayesian statistics in the trial protocol to reduce the required number of control patients [70] and using real-world evidence (RWE) as a substitute for an external control in a single-arm trial.[71,72]

In response to the COVID-19 pandemic, there have been several multi-site and even multi-national adaptive platform trials for therapeutics.[73,74,75] The ACTIV-3/TICO Working Group is a platform built to facilitate effective mounting of placebo-controlled multicenter trials of therapeutics for COVID-19. The REMAP-CAP trial is a multifactorial adaptive platform trial screening therapeutics for Community Acquired Pneumonia. I-SPY COVID-19 is an adaptive platform trial screening therapeutics for COVID-19 patients in Intensive Care Units. These are excellent examples of innovation in clinical trials and represent the current state of the art well. Even with the use of adaptive randomization based on Bayesian statistics, which greatly reduces the number of patients required per arm, these trials have been limited in their ability to quickly enroll enough patients to power their arms to completion, in part due to the challenge of locating sites

[60] Keusch GT, McAdam K, Cuff PA, Mancher M, Busta ER. Integrating Clinical Research into Epidemic Response: The Ebola Experience. National Academies Press; 2017. doi:10.17226/24739.

[61] Muller MP, McGeer A, Straus SE, Hawryluck L, Gold WL. Clinical Trials and Novel Pathogens: Lessons Learned from SARS. *Emerg Infect Dis*. 2004;10(3):389-394. doi:10.3201/eid1003.030702

[62] Wilder-Smith A, Vannice K, Durbin A, et al. Zika vaccines and therapeutics: Landscape analysis and challenges ahead. *BMC Med*. 2018;16(1):1-15. doi:10.1186/s12916-018-1067-x

[63] Petkova E, Antman EM, Troxel AB. Pooling Data from Individual Clinical Trials in the COVID-19 Era. *JAMA*. 2020;324(6):543-545. doi:10.1001/jama.2020.13042

[64] Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7

[65] Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: Issues to consider. *Trials*. 2012;13(1):1-8. doi:10.1186/1745-6215-13-132

[66] Bangdiwala SI, Bhargava A, O'Connor DP, et al. Statistical methodologies to pool across multiple intervention studies. *Transl Behav Med*. 2016;6(2):228-235. doi:10.1007/s13142-016-0386-8

[67] Rocca M, Asare A, Esserman L, Dubman S, Gordon G. Source Data Capture from EHRs: Using Standardized Clinical Research Data 2019.; 2019.

[68] Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and external controls in clinical trials – A primer for researchers. *Clin Epidemiol*. 2020;12:457-467. doi:10.2147/CLEP.S242097

[69] Schmidli H, Häring DA, Thomas M, Cassidy A, Weber S, Bretz F. Beyond Randomized Clinical Trials: Use of External Controls. *Clin Pharmacol Ther*. 2020;107(4):806-816. doi:10.1002/cpt.1723

[70] Dron L, Golchi S, Hsu G, Thorlund K. Minimizing control group allocation in randomized trials using dynamic borrowing of external control data – An application to second line therapy for non-small cell lung cancer. *Contemp Clin Trials Commun*. 2019;16:100446. doi:10.1016/j.conctc.2019.100446

[71] Davies J, Martinec M, Delmar P, et al. Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib. *J Comp Eff Res*. 2018;7(9):855-865. doi:10.2217/cer-2018-0032

[72] Mack C, Christian J, Brinkley E, Warren EJ, Hall M, Dreyer N. When context is hard to come by: external comparators and how to use them. *Therapeutic Innovation & Regulatory Science* Epub November, 2019. DOI: 10.1177/2168479019878672

[73] COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients. ClinicalTrials.gov identifier: NCT04488081. https://clinicaltrials.gov/ct2/show/NCT04488081. Accessed December 4, 2020.

[74] Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community - Acquired Pneumonia. ClinicalTrials.gov identifier: NCT02735707. https://clinicaltrials.gov/ct2/show/NCT02735707. Accessed December 4, 2020.

[75] ACTIV-3: Therapeutics for Inpatients With COVID-19. ClinicalTrials.gov identifier: NCT04501978. https://clinicaltrials.gov/ct2/show/NCT04501978. Accessed December 4, 2020.

geographically near the constantly shifting virus hot spots. They would also benefit from the ability to reduce the number of patients assigned to their control group, freeing up more patients to be enrolled in active arms of the trials.

Adoption of common patient data sets and common control data sets by different trials would permit data integration across different geographic regions and accommodate for racial and ethnic diversity in the population. Even partial integration of results would help address this gap, increase efficiency, and speed clinical trials to fruition. The number of control patients required could also be reduced, increasing trial efficiency and power by boosting the number of patients available to be enrolled in the active arm(s) of each trial.

Concept Proposal

Goals:

A strategy to improve the efficiency of clinical trials in response to a viral epidemic or pandemic could encompass two main goals:

- Increase the agility of trials by making it possible to use data from patients at disparate geographic locations, and potentially combine data from patients enrolled in different trials altogether.
- Share control group patients across multiple trials in order to reduce the number of patients which must be allocated to controls, thus increasing the number of patients available for active arms of trials.

Objectives:

The proposed solution would consist of a method for creating a published and documented "memorandum of understanding" (MOU) defining a data guide or checklist that is used for care and research and is specific to the epidemic or pandemic. This would facilitate data exchange and the sharing of the active and control patient data. Ideally these guides or checklists would be used in clinical care, not just clinical trials. That way all patients being treated could become part of a real-world evidence (RWE) cohort. This approach can be fruitful in addressing multiple questions across a variety of healthcare settings and providers. However, it would be important to identify what types of studies would be facilitated by such a structure. Multi-stage Randomized Controlled Trials (especially those that have active agent "standard of care" control arms) would likely require more infrastructure and a richer, more developed common protocol. Examples of these include the TICO studies in the US[76] and the RECOVERY trial in the United Kingdom.[77] The MOU and data exchange method would cover and specify common data elements collected for each enrolled patient so that:

- Patient data from different geographic locations using the same trial protocol could be integrated and compared (this is already done in multi-site platform trials such as the I-SPY, REMAP-CAP, and ACTIV-3 trials), but even these trials would benefit from the ability to quickly add sites and collect patient data in new geographic regions as the pandemic surges, offsetting enrollment drops in locale where the pandemic has died out).

[76] Clinical Trial Testing Eli Lilly's LY-CoV555 Antibody Against SARS-CoV-2 / COVID-19 Begins. SciTechDaily. https://scitechdaily.com/clinical-trial-testing-eli-lillys-ly-cov555-antibody-against-sars-cov-2-covid-19-begins/. Published September 4, 2020. Accessed December 4, 2020.
[77] Normand, S-LT. The RECOVERY Platform. *N Engl J Med*. 2020 Jul 21; NEJMe2025674.

- Patient data from different trials examining the same active agent or device could be exchanged and integrated.
- The MOU could begin the process of planning for creation of a standing national capacity for evaluation of medical products, especially for existing drugs that might usefully be repurposed, to address future pandemics and emerging pathogens.

A definition or "data dictionary" of common data elements would be needed, including standardized patient demographics, critical clinical variables, electronic phenotypes relevant to the disease (e.g. diagnosis, risk factors, complications), disease scales (e.g., the WHO COVID-19 scale which includes disease status and progression and thus enables calculation of time to recovery), laboratory values, adverse clinical events and secondary endpoints. Therapeutic agents, route of administration, and dosing would also be part of the common data elements for each trial.

Note that not all reported and shared endpoints need be the actual endpoints for the trial (e.g., trial endpoint is mortality/morbidity, but days on ventilator could also be reported, as that may be a relevant endpoint for a different trial). If each trial collected this minimal essential data set, for patients in their active arm(s) as well as for patients in their control or standard of care arm, trials would have comparable and interchangeable data.

One key benefit of the memorandum of understanding/data guide approach would be collecting the defined common data elements for the control or standard of care patients (which would also document how treatment for the control patients may have changed over time due to improvements or changes in the standard of care). Another benefit of defined data collection from "standard of care" patients would be the ability to use them in a RWE control arm. Currently the lack of standardized data collection mechanisms and repositories, along with a lack of payer reimbursement for the collection of this data, inhibits the implementation of RWE control arms and will need to be addressed.

While diseases are variable, and outcomes vary by region, likely due to differences in resources available to individual sites, local surge conditions, etc., there should be a way to assess basic information about patients, and ideally, most trials would be master protocols with shared control arms. Each participating trial could then use the shared control data set in partial or complete replacement of its own control group, or as a "synthetic control." Ultimately each trial would not have to use a significant fraction of their available patient population as control subjects and could instead enroll those patients into active arms of their trial.

A final potential outcome of the proposed solution would be a method for the creation of "virtual trial arms." A virtual trial arm would include the common data elements described above, combined with the common control standard proposed, along with an overarching randomization protocol to account for the placement of patients into one of the real or virtual active arms of the trial or into the shared or synthetic control arm. This would then make it possible, for example, to include an agent from an independent single arm Randomized Control Trial as a virtual arm in a multi-agent platform trial.

One of the other barriers to expanding networks of trials is that each site or group of related sites must review the protocol, get IRB approval or set up a central IRB process, and get training for their physicians to be able to conduct trials. In the US there is no national infrastructure that makes it easy to set up a network of sites to rapidly test new agents such as occurred with the RECOVERY trial in the UK. In order to prepare to extend trials to sites where patients are ill and being treated, the process of helping sites get trained for participation in clinical research must be streamlined,

for example through the creation of a concierge service to help onboard sites, review and sign contracts, and support sites with experiential training and oversight. From the site side of the equation, there should be willingness to sign on to a standard contract and to work with the trial sponsor to streamline the process. From the trial sponsor side, there needs to be a highly efficient process to minimize the time and effort required to go through the steps for site activation, while still maintaining the appropriate quality controls. Payers should provide payment to providers for using the data dictionary or standardized checklists for data collection of the common data elements for all epidemic or pandemic patients being treated (e.g., all patients who test positive for COVID-19). This would increase the willingness of all healthcare providers to adopt such tools, and greatly increase the quantity of clinical data available for research purposes. This will require a different attitude and approach by all actors across the continuum of care. There should be a greater sense of urgency during an epidemic or pandemic, particularly because of the variable nature of the disease, and uncertainty about how long a given surge might last. Wasting time on duplicative work that is not directly related to the safety of patients is intolerable during a crisis and all parties need to come together to streamline the process of rapidly implementing effective clinical trials.

Feasibility:

Potential groups and organizations that could work on defining the process for creating the memorandum of understanding and data guide might include the following organizations and programs:

- I-SPY TRIAL Consortium. Sponsored by the Quantum Leap Healthcare Collaborative and over 20 academic medical centers across the USA, the I-SPY TRIALS are designed to decrease the time, the cost, and the number of patients required to efficiently bring new drug therapies to patients who need them urgently.
- OneSource Project. The OneSource initiative seeks to integrate care and research by streamlining the collection and distribution of patient health data. It is a collaboration between investigators at the University of California San Francisco (UCSF)/Stanford Centers of Excellence in Regulatory Science and Innovation (CERSI),[78] the US FDA, and the Quantum Leap Healthcare Collaborative.
- Duke University - Margolis Center for Health Policy. Duke-Margolis brings together the university's leading research, education and engagement capabilities to inform policymaking and implementation for better health and health care. Duke-Margolis is working with several adaptive platform clinical trials (such as I-SPY COVID, REMAP-CAP, and ACTIV-3) to coordinate the accrual of patients in rural areas through integrated delivery networks (IDNs).
- The US Department of Health and Human Services (HHS), the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), and Operation Warp Speed could also be key partners in promoting the kinds of collaborative efforts described above and help to find ways to reduce barriers for healthcare provider participation in clinical trials.

[78] FDA and CERSIs Collaborate to Advance Regulatory Science. U.S. Food and Drug Administration. https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis. Published 2020. Accessed December 5, 2020.

Plank # 3. Real-world Evidence Solutions for Converting COVID-19 Diagnostics from EUAs to 510(k)

Gap Analysis

The COVID-19 pandemic necessitated bringing testing technology to clinical medicine quickly. This was made possible on February 4, 2020 through a declaration by the U.S. Secretary of Health and Human Services on the emergency use of diagnostics for SARS-CoV-2. The Food and Drug Administration (FDA), under Emergency Use Authorization (EUA), was able to expedite access to diagnostic tests during emergencies without those tests meeting all the standards required by the existing regulatory framework.[79] Molecular diagnostic tests were developed, validated, and deployed under the EUA within weeks rather than months or years. By December of 2020 twelve antibody tests had been authorized under an individual EUA, and over 200 antibody tests are currently the subject of a pre-EUA or EUA review.

The FDA succeeded in permitting earlier test availability, while recognizing that due to the EUA's less-rigorous evidence standard some COVID-19 testing ultimately proved to have performance problems or to be poorly validated. The FDA corrected such cases and continues to evaluate. This concern about the quality of new testing must be understood within the inherent limitations of testing. COVID-19 diagnostic tests may be less accurate in asymptomatic or low-risk populations and in persons who shed little virus or are early or late in the course of illness. The positive and negative predictive value of a test must also be factored into clinical decision making and patient counseling. All tests will produce at least some false results. Even a high-performing antibody test, when used on individuals in a population that does not have many cases of COVID-19 infection, a population with low disease prevalence, may produce as many or more false results as true results because the likelihood of finding someone who has been infected is very small. This doesn't indicate that the test is faulty but is due to the inherent limitations of such tests. It may be necessary for some individuals to have two serology tests performed to generate reliable results. Antibody testing should only be used as part of a well-conceived testing plan and the results should always be interpreted by the appropriate experts who understand its limitations and use test results as just one piece of data to inform clinical decision making.

The 21st Century Cures Act has directed the FDA to consider the use of real-world experience for further evaluation, a strategy that may make it possible to convert the EUA status of *in vitro* diagnostics to a traditional 510(k) pathway. The FDA will continue to take steps to appropriately balance assurances that an antibody test is accurate and reliable with timely access to such tests as the continually evolving circumstances and public health needs warrant. The concept proposal that follows provides some direction for this process.

Concept Proposal

<u>Goal:</u>

Use real-world evidence (RWE) to evaluate *in vitro* diagnostics that have been approved under EUA to consider conversion to 510(k) status.

[79] Shuren J, Stenzel T. Covid-19 molecular diagnostic testing-lessons learned. *N Engl J Med*. 2020;383(17):e97.

Objectives:

- Identify manufacturers and products to collaborate to evaluate *in vitro* diagnostics currently marketed under an EUA using RWE.
- Identify RWE data sources in clinical systems to evaluate *in vitro* diagnostics currently marketed under an EUA.
- Develop agreed-upon methods to analyze RWE to evaluate in vitro diagnostics currently marketed under an EUA.
- Facilitate the implementation of Systemic Harmonization and Interoperability Enhancement for Lab Data (SHIELD) standards in RWE clinical data systems to streamline aggregation of data and the review process.
- Widely share learnings for practical RWE applications for FDA regulatory submission process.

Measures of Success:

This project can be judged successful by creation of a predictable regulatory pathway that can be used as part of a post-market consideration to evaluate the safety and efficacy of *in vitro* diagnostics. The successful provision of additional evidence enables this transition from EUA to 510(k) status.

Methods:

- Proposed industry partners: Companies (sponsors) that produce *in vitro* diagnostics (e.g., Roche and Fisher) have agreed to participate in a COVID RWE Work Group formed by the Medical Device Innovation Consortium (MDIC).
- Clinical data partners: the COVID RWE Work Group is working with major health systems to bring together different parts of the data system, including Laboratory Information Systems (LIS) and electronic health records (EHR). The COVID RWE Work Group is aiding clinical systems to adopt the HHS mandated coding standards (SHIELD) for COVID-19 testing data.
- Regulatory science tools: CDRH, MDIC, and MDEpiNet are already working together on epidemiological and statistical tools to use RWE to evaluate in vitro diagnostics. Protocols have been developed.
- Protocol development: Device companies (sponsors) will engage in a pre-competitive discussion to suggest ways that RWE can be used to support pre-post market balance. The goal of these exercises will be the development of consensus about study designs that can be used for regulatory submissions to enable EUA to 510(k) conversion. With this approach different sponsors will share proposed study designs with the FDA sequentially. A publication focused on lessons learned will be released at the end of the exercise.

Feasibility:

Currently this critical project has not been funded. This work may find support from a variety of funding agencies including PCORTF. Sponsors will incur customary expenses with the regulatory process. Additional stakeholders may be approached to fund this activity.

Plank # 4. The Federal Role in Building Real-World Evidence Infrastructure: Creating an "FCC for Health IT"

Gap Analysis

The pandemic has laid bare the weaknesses of our national public health data enterprise despite decades of intensive digitizing.[80] Lack of syntactic and semantic interoperability, inapt documentation, and security problems have confounded efforts to improve the system.[81] Lack of interoperability is a major barrier to using data collected as part of routine care to respond to the pandemic.[82] The inability to trace the provenance of data is another barrier to the use of real-world evidence (RWE).[83] The creation of a real-world data (RWD) system to address the pandemic cannot progress without work on interoperability.

Recent legal changes and regulatory steps by HHS, including the 21st Century Cures Act[84], the new ONC Information Blocking rule[85], and the ONC's Health IT Certification Program[86] offered only a piecemeal approach to a much greater problem. For instance, many hospitals were unprepared for the requirement to make clinical notes directly and nimbly available to patients.[87],[88] Only a well-conceived, cabinet-level government agency can provide the essential framework and standards environment in which health IT can flourish. The vision of a "plug and play" health care data environment will remain elusive until these issues are addressed.

Real-world evidence (RWE), including data collected as part of routine clinical care, has been heralded as a solution to many of the woes of our medical system.[89] A popular view suggests that a wealth of untapped data – from electronic medical records, medical imaging, mobile apps, and, more recently, low-cost gene sequencing and wearable devices, unlocked using artificial intelligence, cloud computing and blockchain – is a path to better diagnostics, personalized treatments, and early disease prevention for millions.[90] Comprehensive interoperability, a "plug

[80] Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. *N Engl J Med*. 2020;382(23):e82.

[81] Gliklich RE, Leavy MB, Dreyer NA. Selecting and Defining Outcome Measures for Registries. In: *Registries for Evaluating Patient Outcomes: A User's Guide. 4th Edition*. Agency for Healthcare Research and Quality (US); 2020. (Prepared by L&M Policy Research, LLC, under Contract No. 290-2014-00004-C with partners OM1 and IQVIA) AHRQ Publication No. 19(20)-EHC020. Rockville, MD: Agency for Healthcare Research and Quality; September 2020. Registries for Evaluating Patient Outcomes: A User's Guide: 4th Edition | Effective Health Care Program. Effective healthcare.ahrq.gov. https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/users-guide. Published 2020 Accessed December 4, 2020.

[82] Schneider E. Failing the Test — The Tragic Data Gap Undermining the U.S. Pandemic Response. *N Engl J Med*. 2020;383(4):299-302. doi:10.1056/nejmp2014836

[83] Miksad, Rebecca A., and Amy P. Abernethy. "Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality." *Clinical Pharmacology & Therapeutics* 103.2 (2018): 202-205.

[84] Avorn, Jerry, and Aaron S. Kesselheim. "The 21st Century Cures Act--Will It Take Us Back in Time?." *The New England journal of medicine* 372.26 (2015): 2473-2475.

[85] Information Blocking | HealthIT.gov. Healthit.gov. https://www.healthit.gov/topic/information-blocking. Published 2021. Accessed January 28, 2021.

[86] Sheet, Final Rule Fact. "ONC Health IT Certification Program: Enhanced Oversight and Accountability."

[87] HHS Finalizes Historic Rules to Provide Patients More Control of Their Health Data. HHS.gov. https://www.hhs.gov/about/news/2020/03/09/hhs-finalizes-historic-rules-to-provide-patients-more-control-of-their-health-data.html. Published 2020. Accessed December 5, 2020.

[88] 1st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program. Federal Register.https://www.federalregister.gov/documents/2019/03/04/2019-02224/21st-century-cures-act-interoperability-information-blocking-and-the-onc-health-it-certification. Published 2020. Accessed December 5, 2020.

[89] Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us. *N Engl J Med*. 2016;375(23):2293-229

[90] Lehne, Moritz, et al. "Why digital medicine depends on interoperability." NPJ digital medicine 2.1 (2019): 1-5.

and play" environment, may help medicine in the way it has made possible international banking on cell phones, the "internet of things," and online shopping. An interoperable national health information system has not materialized, however, because of 1) clinical care in data silos, 2) incompatible health IT systems, and 3) proprietary software that make health information difficult to exchange, analyze, and interpret. Clinical decision support tools being developed also require interoperability of data within and between institutions.

A strong government regulatory presence is essential to the success of health IT of the kind that has been achieved by the global telecommunications business. The Federal Communications Commission (FCC), with other agencies including the Consumer Product Safety Commission and the National Council on Disability, works to create standards that make possible a huge and lucrative business sector.[91] The robust debate about the appropriate role in regulating that industry attests to how successful FCC efforts have been. In the health sector, however, after decades of deregulation and weakening of the government's role, the pandemic has made it clear how little has been achieved in health IT despite intensive investment by both the public sector and industry.

Discussion is needed concerning what agencies, through what sort of authority, with what resources, and through which processes, can carry out this work. The government role in Health IT includes convening stakeholders to decide upon pre-competitive needs of the Health IT ecosystem, and creating binding standards for interoperability and safety. The SHIELD (Systemic Harmonization and Interoperability Enhancement for Laboratory Data)[92] experience described below has provided a model for success, using a "bottom up" effort to create technical standards satisfactory to stakeholders, followed by a "top down" action by government to apply those standards. Government should also support the work of the ecosystem to come together in such a way that the needs and constraints of each stakeholder are understood by all. The government role in implementation and enforcement must also include communications, monitoring and evaluation, and funding support.

The role of the private sector cannot be underestimated in this enterprise. The economic and sociological literature has made clear that complex issues benefit from what have been called strategically coordinated networks.[93] Successful sectors of the new economy around the globe have understood that coordination is essential. Government's role is to provide complementary investment and provide a forum in which stakeholders can come together to find solutions to shared problems. Examples come from the California biotech industry and German Baden-Württemberg model, highly productive sectors that have benefited from strategically coordinated networks.[94] Work in networks emphasizes cooperation, specifically partners' commitment and alignment of interests, as the key determinant of collaborative success. [95]

AI provides another example of how a government role in building strategically coordinated

[91] Tanenbaum M. The historical evolution of US telecommunications. *Technol Soc*. 1993;15(3):263-272.
[92] MDEpiNet. https://www.mdepinet.net/shield Accessed January 23, 2021
[93] Hage J. *Knowledge Evolution and Societal Transformation: Action Theory to Solve Adaptive Problems*. Anthem Press; 2020
[94] Germany: rebalancing the coordinated market economy in times of disruptive technologies — Policy Network. Policy Network. https://policynetwork.org/opinions/essays/germany-rebalancing-coordinated-market-economy-times-disruptive-technologies/. Published 2020. Accessed December 5, 2020.
[95] Gulati R, Wohlgezogen F, Zhelyazkov P. The two facets of collaboration: Cooperation and coordination in strategic alliances. *Acad Manag Ann*. 2012;6(1):531-583

networks may function to promote scientific and economic development.[96] To counter fragmentation of our current regulatory frameworks around AI and effectively coordinate the mitigation of AI risks we need coordinated governance. Development and application of AI requires a national and global governance mechanism that includes the largest economies and their highest political representatives. Without global coordination, national efforts to regulate AI may become an instrument of strategic competition and rivalry.

Ethical Issues:

The work proposed here to create a new regulatory landscape must be explicit about the ethical issues it must address. There tends to be broad agreement in the health IT space on which values should be emphasized. The intersection of health information technology and ethics has a solid track record[97] in identification of core values for addressing ethical issues and for providing guidance on policy.

The failures of the world's COVID-19 response are familiar issues for the ethics-and-informatics community including:

- Absence of a robust interoperable data collection and curation plan and process
- Limited data sharing and collaboration on analysis
- Failures of trust related to data collection, sharing and analysis
- Lack of guidance on use of decision support systems, or identification of appropriate uses and users of existing data
- Absence of a trusted broker to guide and mediate
- Absence of funding
- Lack of adequate data to understand social determinants and racial and ethnic disparities in health

The FDA, through its Digital Health Center of Excellence,[98] its Network of Digital Health Experts (NoDEx)[99] and the Network's partner organizations[100] has taken steps to seek external guidance to address some of these issues. A trusted and vigorous semi-autonomous body would be able to provide expert guidance on the ethical and policy issues raised by COVID-19 and, indeed, all health information technologies. Such an entity would parallel the Ethical, Legal and Social Issues (ELSI) component of the Human Genome Program and provide a ready source of support for the Cabinet-level entity envisioned here.

Building on successes:

Three successful government-supported models for standards of interoperability and security have developed that may guide more comprehensive efforts: Digital Imaging and Communications in

[96] Jelinek T, Wallach W, Kerimi D. Policy brief: the creation of a G20 coordinating committee for the governance of artificial intelligence. *AI Ethics*. Published online 2020:1-10.
[97] Goodman KW. *Ethics, Medicine, and Information Technology: Intelligent Machines and the Transformation of Health Care*. Cambridge University Press; 2016.
[98] Digital Health Center of Excellence. U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/digital-health-center-excellence. Published 2020. Accessed December 5, 2020.
[99] Network of Digital Health Experts. U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/digital-health-center-excellence/network-digital-health-experts. Published 2020. Accessed December 5, 2020.
[100] Network of Experts Program: Connecting the FDA with External Expertise. U.S. Food and Drug Administration. https://www.fda.gov/about-fda/center-devices-and-radiological-health/network-experts-program-connecting-fda-external-expertise#participants. Published 2020. Accessed December 5, 2020.

Medicine (DICOM); SHIELD; and the ISO Remote Connected Care and Mobile Health project. The proposed "FCC for Health IT" should build on these successes.

The Digital Imaging and Communications in Medicine (DICOM) standard has become the most widely implemented and supported communications standard for medical imaging.[101] The DICOM standard enables health-related computing applications by ensuring interoperability between imaging devices and Picture Archiving and Communications Systems (PACS). Interoperability between imaging devices and between imaging systems is not a trivial issue. Physical connectivity requires sharing a complete transfer protocol, but the communication of information content requires sharing the semantic context. Today, it is unusual to purchase an acquisition modality that does not provide a standard DICOM interface for the storage of images across the network. All modern PACS provide a standard DICOM interface to allow the reception of images from modalities. Although at present it is not simply "plug and play" for modalities to operate within a PACS environment, there has been considerable progress.

"SHIELD as a public private partnership has been established to address […] interoperability barriers […]. By improving the semantic interoperability of laboratory data within and between institutions, diagnostic information can be used to better support clinical decisions. SHIELD supports the provision of vetted and harmonized codes from manufactures/industry to laboratories; this enables consistent representation in laboratory information systems and downstream to electronic health records, achieving cross-institutional semantic interoperability. The mission of SHIELD is implementation of harmonized application and to advance innovation and reduce burdens to healthcare. The shared goal for all SHIELD stakeholders has developed out of the shared needs of data producers and end users.

SHIELD provides an authoritative source for coding by working with over 70 stakeholders including: major IVD Manufacturers, commercial and laboratory laboratories, Association of Public Health Labs, (APHL), EHR vendors, standards developers, PEW Charitable Trusts, NEST/MDIC, College of American Pathologists, MDEpiNet, FDA (CDRH, CDER, CBER), CDC, NIH, ONC, CMS, and the VA. The many standards organizations come together around this consultative effort and include organizations working with data standards (including LOINC, SNOMED, CT UCUM, UDI, LIVD[102], and FHIR).

SHIELD took a major step forward when HHS directed that harmonized codes for COVID-19 tests be nationally disseminated. A new requirement, which went into effect August 1, 2020 , will help provide crucial information needed to monitor and fight the pandemic nationally.[103] Public Law 116-136, § 18115(a), the Coronavirus Aid, Relief, and Economic Security (CARES) Act, requires "every laboratory that performs or analyzes a test that is intended to detect SARS-CoV-2 or to diagnose a possible case of COVID-19" to report the results from each such test to the Secretary of the Department of Health and Human Services (HHS). In addition, the statute authorizes the Secretary to prescribe the form and manner, and timing and frequency, of such

[101] Kahn C, Carrino J, Flynn M, Peck D, Horii S. DICOM and Radiology: Past, Present, and Future. *Journal of the American College of Radiology*. 2007;4(9):652-657. doi:10.1016/j.jacr.2007.06.004

[102] LOINC In Vitro Diagnostic (LIVD) Test Code Mapping for SARS-CoV-2 Tests | CDC. Cdc.gov. https://www.cdc.gov/csels/dls/sars-cov-2-livd-codes.html. Published 2020. Accessed December 5, 2020.

[103] COVID-19 Pandemic Response, Laboratory Data Reporting: CARES Act Section 18115. Hhs.gov. https://www.hhs.gov/sites/default/files/covid-19-laboratory-data-reporting-guidance.pdf. Published 2020. Accessed December 5, 2020.

reporting. A policy was issued in June 2020 that outlines the requirements for data submission to HHS as authorized under this law prescribing SHIELD as the authoritative source."[104]

The International Organization of Standardization (ISO) effort to promote interoperability and security of data from Remote Connected Care and Mobile Health is a crucial contribution to combating the pandemic. Telehealth is a critical need highlighted by COVID-19; an ISO effort is developing to address interoperability and safety issues for the diverse devices involved. Remote care also provides new avenues for designing virtual trials and accumulating interoperable data for real-world evidence (RWE) to facilitate important public health objectives including surveillance, epidemiology, analytics, medical device innovation. The CRN approach circumvents the limitations of traditional registries and data repositories by building linked data systems from multiple sources. These limitations can also be remedied by collaboration with Standard Development Organizations (SDOs) such as HL7, ISO TC 215, IEEE Point of Care Devices/Personal Health Devices (PoCD/PHD) that harmonize standards and data for various health informatics and interoperability tasks.

Towards a call to action:

The current high-water mark for a practical vision in this area is the Institute of Medicine's Learning Health Care System (LHCS) of over a decade ago.[105] While that effort paved the way for major steps towards improving health IT, the now classic report falls short not having fully articulated the needs of a bona fide "plug and play" environment. To create a LHCS, there must be a data infrastructure that is interoperable and secure. A literature has grown up concerning the limitations of the current LHCS strategy and recommendations to advance parts of health IT.[106,107] The vision of a LHCS has indeed evolved, fledged a new domain for scholarship and includes recognition of the need to ensure that "Best practice knowledge derived from these data is immediately available to support health-related decisions by individual members of society, care providers, and managers and planners of health services."[108] A "2.0" version of the LHCS should incorporate the many recommendations that have followed it and the broader program of LOGICA Health, the comprehensive framework and organizations supporting it.[109]

The gap analysis suggests that the next step towards a secure and interoperable environment is the creation of a federal entity to develop and support implementation of a framework for the Health IT enterprise to thrive in. The concept proposal of this plank begins work for a "call to action" for the legislative action and regulatory structures needed to better respond to pandemics and enhance the US health IT system to be able to address the major challenges in healthcare ahead of us. The "call to action" should address composition and roles of stakeholders in a governance structure, reconfiguration of current government agencies and authorities, and coordination of current standardization efforts.

[104] Forthcoming manuscript FDA, Waters et. al

[105] Olsen L, Aisner D, McGinnis JM. The learning healthcare system: workshop summary. Published online 2007.

[106] Bitton A, Flier L, Jha A. Health Information Technology in the Era of Care Delivery Reform. *JAMA*. 2012;307(24). doi:10.1001/jama.2012.6663

[107] Buntin M, Jain S, Blumenthal D. Health Information Technology: Laying The Infrastructure For National Health Reform. *Health Affairs*. 2010;29(6):1214-1219. doi:10.1377/hlthaff.2010.0503

[108] Friedman C, Allee N, Delaney B et al. The science of Learning Health Systems: Foundations for a new journal. *Learn Health Syst*. 2016;1(1):e10020. doi:10.1002/lrh2.10020

[109] Logica – information at the speed of life. Logicahealth.org. https://www.logicahealth.org. Published 2020. Accessed December 5, 2020.

Concept Proposal

Goal:

A task force should be convened to produce a white paper outlining a blueprint for a national body to guide data interoperability standards and security in order to enable rapid development of health IT that supports pandemic/emergency preparedness, healthcare delivery, quality assurance, research, medical product development, surveillance, and cost containment.

Objectives:

- Identify and engage key stakeholders for contributions to the white paper.
- Identify concrete use cases that will illustrate the importance of the development of regulatory powers to improve health data interoperability, including those for pandemic and emergency responses.
- Facilitate collaboration around structure and function of a national entity to direct national health data standards, technology standards, and data safety standards.
- Initiate the coalition-building necessary to move the work to legislative action.

Methods:

The University of Miami Institute for Data Science and Computing provides an outstanding base to initiate a national task force to be charged with the proposed white paper. The white paper may take the form of a "call to action" publication in a peer reviewed journal. This discussion of policy related to the promotion of interoperability may usefully be developed as a theme in peer reviewed journals and trade publications read by leaders in big tech. Promoting a new approach to healthcare in the US that comprises development of a pre-competitive space that brings together the multiple stakeholders is an essential step. Medical products industries have started this trend with the creation of Vulcan,[110] a consortium of stakeholders devoted to the promotion of syntactic interoperability.

The call to action should propose creation of a legal entity with regulatory authority that will drive development of health IT agencies, including state and regional Health Information Exchanges (HIE), state claims databases, and state vaccine registries.

Feasibility:

The Task Force and white paper recommended here may be launched by the Miami Institute for Data Science and Computing (IDSC) to prepare a peer reviewed article. A coalition to promote the action recommended here will require a larger effort and necessitate the commitment of many Health IT stakeholders to move forward. Congressional action regarding the current pandemic and preparation for future emergencies is hard to predict and the way a coalition might come together to promote these changes has not been determined.

[110] Vulcan | HL7 International. Hl7.org. http://www.hl7.org/vulcan/. Published 2020. Accessed December 5, 2020.

Plank # 5. Creating a COVID-19 Module: Advancing the Evidence Base for Coordinated Registry Networks

Gap Analysis

During the COVID-19 pandemic, many national registries began capturing COVID-19-related data, but these efforts are not harmonized yet. The Coordinated Registry Networks (CRN)[111] infrastructure is uniquely suited to address the needs of clinical specialty societies and their registries to respond to the pandemic.

CRN have been a key strategy identified by the National Medical Device Registry Task Force (NMDRTF)[112] to advance the real-world evidence (RWE) through registry-based harmonized data sources linkable to other clinical data such as EHRs, administrative claims, and Patient-Generated Health Data (PGHD) including Patient-Reported Outcomes (PROs), wearables or other digital health technologies. The CRNs with their deep roots in professional medical societies and interventional care and coordinated by the Medical Device Epidemiology Network (MDEpiNet) have already produced a number of common data elements (CDEs), Fast Healthcare Interoperability Resources (FHIR) platforms and implementation guides (IGs) (vascular, orthopedic, prostate ablation, women's health, acute ischemic stroke).

This concept proposal advances the COVID-19 evidence base by enhancement of CRNs through integration of PGHD. This project will leverage five recently funded PCORTF (an HHS funding program) projects including: (1) FDA/ONC/NLM project to establish interoperable Women's Health Technology[113] (WHT-CRN) including the FHIR IG development and pilot testing; (2) FDA project to expand the WHT-CRN learnings to facilitate maturation of legacy registries to CRNs in 12 high priority clinical areas;[114] (3) AHRQ and ONC[115] project to develop and test the PRO FHIR IG;[116] (4) FDA-led effort to harmonize lab data via SHIELD[117] partnership; and (5) MedMorph,[118]

[111] Coordinated Registry Networks. Mdepinet.net. https://www.mdepinet.net/coordinated-registry-networks. Published 2020. Accessed December 5, 2020.

[112] National Medical Device Registry Task Force. Mdepinet.org. http://www.mdepinet.org/wp-content/uploads/Recommendations-for-a-National-Medical-Device-Evaluation-System_24-Aug-2015.pdf#:~:text=The%20National%20Medical%20Device%20Registries%20Task%20Force%20was,time%20and%20support%20from%20Jeffrey%20Shuren%2C%20William%20Maisel%2C. Published 2020. Accessed December 5, 2020.

[113] Developing a Strategically Coordinated Registry Network (CRN) for Women's Health Technology. ASPE. https://aspe.hhs.gov/developing-strategically-coordinated-registry-network-crn-womens-health-technology. Published 2020. Accessed December 5, 2020.

[114] Bridging the PCOR Infrastructure and Technology Innovation through Coordinated Registry Networks (CRN) Community of Practice. ASPE. https://aspe.hhs.gov/bridging-pcor-infrastructure-and-technology-innovation-through-coordinated-registry-networks-crn-community-practice. Published 2020. Accessed December 5, 2020.

[115] Advancing the Collection and Use of Patient-Reported Outcomes (PROs) through Health Information Technology (IT). ASPE.https://aspe.hhs.gov/advancing-collection-and-use-patient-reported-outcomes-pros-through-health-information-technology-it. Published 2020. Accessed December 5, 2020.

[116] Patient Reported Outcomes FHIR Implementation Guide. http://hl7.org/fhir/us/patient-reported-outcomes/2018Sep/index.html. Published 2020. Accessed December 5, 2020.

[117] SHIELD- Standardization of Lab Data to Enhance Patient-Centered Outcomes Research and Value-Based Care. ASPE. https://aspe.hhs.gov/shield-standardization-lab-data-enhance-patient-centered-outcomes-research-and-value-based-care. Published 2020. Accessed December 5, 2020.

[118] Making Electronic Health Record (EHR) Data More Available for Research and Public Health. ASPE. https://aspe.hhs.gov/making-electronic-health-record-ehr-data-more-available-research-and-public-health. Published 2020. Accessed December 5, 2020.

the CDC-led effort to advance the use of EHR infrastructure in research.

Concept Proposal

Goals:

- Create and/or harmonize the COVID-19 module within the national CRNs to include COVID-19 relevant testing and patient management data.
- In select CRNs, link the relevant PGHD, including apps and wearables, to other data sources within the CRN such as registry, claims and EHRs.
- Showcase an example of COVID-19-relevant CRN data sharing by diverse stakeholders through blockchain-enabled FHIR platform.
- Evaluate the utility of newly created infrastructure through a series of demonstration projects assessing the impact of COVID-19 in select chronic diseases and specialty practices within CRNs.

The CRNs, enriched by PGHD, will add to PCOR capacity to study the impact of COVID-19 across many vulnerable populations and types of interventional care. The end users will include: clinicians (facilitating better and faster decision-making and risk predictions), industry (creating potential venue for RWE for regulatory submissions), regulators (by generating a comprehensive understanding of post-market landscape), policy/decision makers, including insurers (by helping to guide the decisions for current and future waves of epidemics), the PCOR researchers (by enriching data sets to study COVID-19's public health impact), and most importantly, our patients (incorporating the patient perspective into traditional data sources).

Objectives:

- Develop a module for adoption by all CRN to collect data about COVID-19 diagnosis, presentation, treatment, and vaccination.
- Incorporate PGHD from mobile apps and wearables into select CRNs.
- Strengthen the integration of the PGHD by integration of blockchain technology that supports consent-based contractual agreements for traceable and auditable data within select CRNs within High Performance Integrated Virtual Environment (HIVE).
- Conduct prototype analyses on the effect of COVID-19 on select chronic diseases and specialty practice within CRN infrastrcuture.

Methods:

- Review and assess the COVID-19 modules within the existing CRNs that represent large populations of medically vulnerable patients, including those experiencing racially or ethnically-based disparities in care and outcomes, and harmonize them using a modified

DELPHI approach.[119,120]

- Modify existing PGHD FHIR IGs to create optimal domains in the select national CRNs (e.g. cardiac, vascular, abdominal, urology, gynecology, plastic surgery, neurology and hematology).
- Integrate state-of-the-art permission-based blockchain to High Performance Integrated Virtual Environment (HIVE) to link relevant PGHD to other CRN data.
- Study effects of COVID-19 using novel analytical approaches using linked datasets.

Feasibility:

The project will build on the strategic investments and existing relationships between FDA Centers, other federal agencies (AHRQ, ONC, NIH, VA, ASPE, CDC and OASH), and other RWE ecosystem partners in clinical, informatics, methodology, data science, and patient science across a variety of healthcare sectors. The existing cooperative agreements with the FDA will facilitate a timely execution of the project as we build on technological platforms developed with existing PCORTF investments that are scalable and robust. The federal and private sector partners have expertise in digital health and patient science, including PROs and PGHD, to advise on the utility of different PGHD and digital health data sources to link with the rest of the CRN data.

[119] Golan R, Bernstein A, Sedrakyan A, et al. Development of a nationally representative coordinated registry network for prostate ablation technologies. *J Urol*. 2018;199(6):1488-1493.

[120] Dreyer NA, Reynolds M, Mack CD, Brinkley E, Petruski-Ivelva N, Hawaldar K, Toovey S, Morris J. Self-reported symptoms from exposure to COVID-19 provide support to clinical diagnosis, triage and prognosis: an exploratory analysis. *Travel Medicine and Infectious Disease* 2020;38:101909.

Plank # 6. Remote Connected Care and Mobile Health in the COVID-19 Era: Solutions for Clinical Practice, RWE, and Trials

Gap Analysis

The current Covid-19 pandemic has created emerging needs for patients and clinicians to communicate with each other and exchange data by digital, remote and virtual means. Numerous studies and reports from relevant literature [121] have shown a dramatic increase in the use of telehealth visits in 2020. This can mitigate patients' and clinicians' risks of exposure to COVID-19 by replacing in-person visits with different virtual clinical workflows when possible.

Many healthcare organizations adopt telehealth approaches to interacting with patients in the hospital as well as tracking the status of patients at home or alternate care institutions. This is termed "Remote Connected Care and Mobile Health (RCC/MH)," a collaborative effort of Standards Data Organizations (SDOs) for medical devices such as International Standards Organization (ISO) TC 215 Health informatics,[122] Health Level 7 (HL7),[123] Institute of Electrical and Electronics Engineers (IEEE),[124] and Integrating the Healthcare Enterprise (IHE)[125,126] RCC/MH provides a flexible set of tools for hospitals, clinics, and home settings, that support patient care, consultation service, and training of patients and healthcare workers. RCC/MH extends the solutions to allow health providers to monitor and diagnose disease remotely and interact with patients virtually. The work enables the care of acutely ill patients outside of the traditional hospital setting, especially in situations where these settings are at or over capacity. In the longer term, RCC/MH interoperability solutions can also have great impact on the design of virtual and safer trials and surveillance and the collection of real-world evidence data for medical product needs.

Changes in the way that healthcare is delivered during this pandemic are needed to reduce exposure to ill persons and minimize the impact of patient surges on facilities. Healthcare systems have had to adjust the way they triage, screen, evaluate, and care for patients using methods that do not rely on in-person services. RCC/MH services help provide care to patients while minimizing the transmission risk of SARS-CoV-2, the virus that causes COVID-19, to healthcare personnel (HCP) and patients.

RCC/MH belongs to the broader context of Telehealth modalities that allow HCP and patients to connect using technology to deliver health care.[127]

- Synchronous modalities include real-time phone or live audio-video interaction typically with a patient using a smartphone, tablet, or computer.

[121] Dorsey, E. Ray, and Eric J. Topol. "State of telehealth." New England Journal of Medicine 375.2 (2016): 154-161
[122] Health informatics. ISO. https://www.iso.org/committee/54960.html. Published 2021. Accessed January 28, 2021.
[123] Health Level Seven International. Overview | HL7 International. https://www.hl7.org/Special/committees/healthcaredevices/overview.cfm. Accessed January 28, 2021.
[124] IEEE 11073-10101-2019 - IEEE Standard for Health informatics--Point-of-care medical device communication - Part 10101: Nomenclature. IEEE SA - The IEEE Standards Association - Home. https://standards.ieee.org/standard/11073-10101-2019.html. Accessed January 28,2021.
[125] Devices. IHE International. https://www.ihe.net/ihe_domains/devices/. Published June 11, 2020. Accessed January 28, 2021.
[126] SES Remote Connected Care and Mobile Health. https://confluence.hl7.org/display/GP/Paper%3A+++SES+Remote+Connected+Care+and+Mobile+Health. Accessed January 28,2021
[127]Telehealth and Telemedicine. Cdc.gov. https://www.cdc.gov/phlp/publications/topic/telehealth.html. Accessed December 5, 2020.

- Asynchronous modalities include "store and forward" technology where messages, images, or data are collected at one point in time and interpreted or responded to later.
- Remote patient monitoring allows direct transmission of a patient's clinical measures such as vital signs remotely (real time, intermittent, continuous etc.),
- Patient monitoring at bedside in ICU (alerts, risk index, reports).

Potential limitations of telehealth should also be considered.[128] Those include the following:

- Interstate licensure challenges and other regulatory issues that may vary by state
- Situations in which in-person visits are more appropriate due to urgency, underlying health conditions, or inability to perform an adequate physical exam
- The need to address sensitive topics, especially if there is patient discomfort or concern for privacy
- Limited access to technological devices (e.g., smartphone, tablet, and computer) needed for a telehealth visit or connectivity issues
- Lack of adoption and implementation of recognized standards
- Need for more enforcement policies/incentives for RCC/MH from Federal/State agencies
- Level of comfort with technology for HCP and patients
- Cultural acceptance of conducting virtual visits in lieu of in-person visits by HCP and patients

Concept Proposal

Goals:

The work will evaluate current interoperability standards, profiles, cases and implementations (HL7/FHIR/IEEE/ISO/IHE/HIMSS) applicability and maturity for Remote Connected Care and Mobile Health Interoperability of specific parameters (heart, respiration, temperature, mental health, imaging, compliance, sleep apnea)[129,130,131] and registries (orthodontics, maternal-fetal, etc.) for high-risk patients affected by the pandemic in different settings, including home care, inpatient hospitals, clinic/ outpatient primary care, and post-acute care.

Measuring and monitoring of conformance, adoption and implementation should be initiated to: generate interoperable harmonized data from devices; reduce data delays and ambiguity; improve the quality of care by making the right data available at the right time, at the right place to the right

[128] Watson, Andrew R., Robert Wah, and Ritu Thamman. "The value of remote monitoring for the COVID-19 pandemic." *Telemedicine and e-Health* 26.9 (2020): 1110-1112.

[129] Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-non-invasive-remote-monitoring-devices-used-support-patient-monitoring-during. Accessed January 28, 2021.

[130] Enforcement Policy for Non-Invasive Fetal and Maternal Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency. https://www.fda.gov/media/137286/Download. Accessed January 28, 2021

[131] Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-digital-health-devices-treating-psychiatric-disorders-during-coronavirus-disease. Accessed January 28, 2021

doctor and the right patient; and make interoperable real-world data (RWD) available for analysis supporting real-world evidence (RWE) for clinical decision-making and innovation. This aim is not only on the technical level but includes medical policy and telehealth payments and industry considerations regarding these data for telehealth.

A Governance Body and Public Private Partnership (GB-PPP) should be initiated to oversee the implementation, adoption, cases, and return on investment of interoperability standards for IEEE 11073 POCD/PHD, HL7 FHIR and ISO TC 215. The GB-PPP will be a mix of industry/government/academia subject matter experts (SMEs) and leaders in the areas of data interoperability, RWE and CRN (clinicians, engineers, informatics, regulatory, medical device industry, research, NIH, FDA, FCC, and OC).

Methods:

- Consultation with HCPs for telehealth and remote care cases.
- Collaboration with ISO TC 215 WG2 interoperability workgroup and the joint HL7-IHE Gemini program[132] or Gemini SDPi+FHIR/HL7 that coordinates HL7 Devices and IHE Devices working groups (SDPi: Service-oriented Device Point-of-care Interoperability).[133]
- Creation of harmonized standards through the well-developed consensus process of IEEE 11073 POCD/PHD, ISO TC 215 and HL7 (FHIR, V2).
- Creation of a grants program to strategically support health systems to implement standards through work with national specialty societies, SDOs and industry.
- Dissemination of harmonized standards to RWE aggregators.
- Piloting of remote monitoring and telehealth devices to support care of patients in specific registries including those with high risk for COVID-19.
- Structuring of data to expand the capacity to care for acutely ill patients, including those in Hospital-at-Home models, and using telehealth for persons under investigation in home quarantine (HCPs and health systems may need to track large populations of same; digital technology can support this).
- Management of the limitations and options for home designed trials (home devices, mobile apps, use of remote data/cloud).
- Monitoring of safeguards for Telehealth (HIPAA, federal/state regulations, CMS payment structure).
- Define a minimum set of safe, effective and secure medical device interoperability standards for RCC/MH solutions to accelerate telehealth implementation for urgent situations in pandemics.

Feasibility:

The project will build on the strategic investments and existing relationships between federal agencies including the FDA Centers, AHRQ, ONC, NIH, VA, CDC, FCC; and other ecosystem partners in SDOs, clinical, informatics, methodology, data science, and patient science across a variety of healthcare sectors. FDA/CDRH SDOs and private sector partners have expertise in digital health and patient science, to advise on the utility of different digital health data sources to

[132] Device Interoperability using SDPi+FHIR. https://confluence.hl7.org/pages/viewpage.action?pageId=66926431 Accessed on January 27, 2021.
[133] SDPi+FHI. https://confluence.hl7.org/pages/viewpage.action?pageId=86969837 Accessed on January 27, 2021

link with the rest of the CRN data. We also plan to institute a small grant competition to attract new investigators to collaborate with the MDEpiNet-coordinated CRN community, as well as other stakeholders in this area, to increase innovative capacity-building approaches such as interoperability in focused areas for remote care and mobile health solutions.

Current projects are ongoing nationally on interoperability of POCD/PHD data harmonization including HL7/IHE/ISO TC 215 and IEEE 11073.

Plank # 7. Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD) and COVID-19

Gap Analysis

Real-world evidence (RWE) has become increasingly important to speed evaluation of care for COVID-19 including diagnostics, therapeutics and vaccines. Interoperability of laboratory data decreases cost and time of traditional data curation of real-world data (RWD). SHIELD has been adopted by the HHS Secretary, creating interoperability of COVID-19 diagnostics for reporting. This interoperable data benefits all RWD efforts involving COVID-19. The next step for SHIELD made possible by this funding will be to address interoperability of other major laboratory domains that are essential for evaluation of therapeutics and vaccines for COVID-19. SHIELD is a well-established consortium of stakeholders established as a public private partnership to develop harmonized coding of laboratory data.

"SHIELD as a public private partnership has been established to address […] interoperability barriers […]. By improving the semantic interoperability of laboratory data within and between institutions, diagnostic information can be used to better support clinical decisions. SHIELD supports the provision of vetted and harmonized codes from manufactures/industry to laboratories; this enables consistent representation in laboratory information systems and downstream to electronic health records, achieving cross-institutional semantic interoperability. The mission of SHIELD is implementation of harmonized application and to advance innovation and reduce burdens to healthcare. The shared goal for all SHIELD stakeholders has developed out of the shared needs of data producers and end users.

SHIELD provides an authoritative source for coding by working with over 70 stakeholders including: major IVD Manufacturers, commercial and laboratory laboratories, Association of Public Health Labs, (APHL), EHR vendors, standards developers, PEW Charitable Trusts, NEST/MDIC, College of American Pathologists, MDEpiNet, FDA (CDRH, CDER, CBER), CDC, NIH, ONC, CMS, and the VA. The many standards organizations come together around this consultative effort and include organizations working with data standards (including LOINC, SNOMED, CT UCUM, UDI, LIVD, and FHIR).

SHIELD took a major step forward when HHS directed that harmonized codes for COVID-19 tests be nationally disseminated. A new requirement, which went into effect August 1, 2020 will help provide crucial information needed to monitor and fight the pandemic nationally. Public Law 116-136, § 18115(a), the Coronavirus Aid, Relief, and Economic Security (CARES) Act, requires "every laboratory that performs or analyzes a test that is intended to detect SARS-CoV-2 or to diagnose a possible case of COVID-19" to report the results from each such test to the Secretary of the Department of Health and Human Services (HHS). […] A policy was issued in June 2020 that outlines the requirements for data submission to HHS as authorized under this law prescribing SHIELD as the authoritative source."[134]

Concept Proposal

This concept proposal builds on strong relationships between federal agencies (CDC, NIH, FDA, OS), the American Society for Hematology (ASH), the Vascular Quality Initiative (VQI), and MDEpiNet.

[134] Forthcoming manuscript FDA, Waters et. al

Goals:

- Develop interoperability of laboratory testing through harmonization of coding for RWE for patient-centered outcomes research on therapeutics and vaccines for COVID-19.
- Leverage the mandate of the HHS Secretary requiring SHIELD for COVID-19 diagnostics to build infrastructure for RWE across HHS agencies and partners.
- Provide implementation tools to support adoption of SHIELD for RWE data systems that serve medically and socially vulnerable populations in pilot studies with clinical specialty societies.
- Decrease the cost and time of data curation and improve the quality of RWD through implementation of harmonized standards for laboratory coding.

Objectives:

- Identify laboratory domains essential for RWE evaluation of therapeutics and vaccines for COVID-19.
- Create harmonized coding to support those domains and related implementation tools.
- Pilot the domains in medically and socially vulnerable populations through work with the registries of the Vascular Quality Initiative and the American Society of Hematology (Sickle Cell Disease and Multiple Myeloma), two national clinical societies, to conduct comparative effectiveness studies of therapeutics and vaccines for COVID-19 in special populations.
- Monitor implementation of SHIELD standards in priority RWE systems.
- Create a small grants program to support implementation in ten additional national society registries.

***Measures of Success*:**

Success can be evaluated through the creation of:

- Harmonized coding instructions for identified lab values (SHIELD LIVD file)
- Implementation Guide and other implementation tools
- An assessment of the quality and extent of the adoption of the LIVD file health systems and laboratories.

Methods:

Methods to create and implement harmonized laboratory standards include:

- Consultation with clinical experts (Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership) to prioritize laboratory domains that are essential for evaluation of therapeutics and vaccines in the post-market setting.
- Creation of harmonized coding standards through the well-developed consensus process of SHIELD.
- Piloting of implementation efforts to include medically and socially vulnerable groups with two national specialty societies (ASH and VQI).

- Use of a small grants program to strategically support health systems' implementation of SHIELD standards through work with national specialty societies.
- Dissemination of harmonized standards to RWE aggregators (PCORnet, Sentinel, registries and other aggregated data systems).
- Assessment of implementation of SHIELD harmonized coding including comparison of data at origin to analytical data sets, tracking data from source to end users.

Feasibility:

Feasibility of prioritization of laboratory domains and creation of harmonized coding strategy has been demonstrated and documented through earlier successes of SHIELD. Feasibility of national adoption of harmonized standards is high, given the priority of COVID-19 and the leverage that coordinated government investments can bring, illustrated by the HHS Secretary's adoption of SHIELD for reporting of diagnostic testing. This project builds on the current role of SHIELD harmonized standards for COVID-19 testing in Rapid Acceleration of Diagnostics (RADx), enabling the next step toward interoperability of RWD infrastructure.

Plank # 8. Blockchain and Artificial Intelligence: Tools to Improve Efficacy of RWE Collection, Aggregation, and Analysis

Gap Analysis

This plank has been contributed to this White Paper by Blockchain and Artificial Intelligence Task Force (BAIT), also convened by MDEpiNet.[135] Improving registry efficiency for data aggregation, curation, safety measures, and analysis will accelerate the development of CRNs (Coordinated Registry Networks). BAIT has identified strategies that can potentially increase data safety and efficiency of certain CRNs using blockchain (BC) and Artificial Intelligence (AI); for example:

- Cybersecurity remains a problem for implantable medical devices that receive and send information. An estimated 82% of healthcare organizations have experienced a cyberattack on their Internet of Medical Things (IoMT)[136] which, if successful, could lead to heavy HIPAA violation fines and direct risk to their patients. Using novel blockchain technology placed at the edge of the medical networks, between the implanted medical device and the internet itself, can improve device data security and provide enhanced data provenance through use of smart contracts.[137]
- Devices that attempt to inject data into a data aggregation system can be filtered using blockchain methods. Data from unverified devices are denied access.[138] Registered devices that report data to the system can be verified through a smart contract, which can be used to retroactively trace all actions performed by the given device.

In these situations, a framework for secure sharing of information among various entities that share connected data will lower costs and speed the flow of data. The current data-sharing system among key players (e.g., federal research institutions, health clinical health data systems, and the FDA) is outdated and still currently relies on human-initiated data requests. These requests take time and do not allow for the granularity many groups would like to see. Moreover, past interactions demonstrated that the data access granularity is not matching the research need. Paying for an entire dataset when only a percentage of said data meets one's criteria is inefficient.

Using a novel blockchain technology that allows for fine-grained access control of data, along with "publish" and "subscribe" features, will ensure that those sharing data do so with only the data they authorize, and those requesting data will get only data of interest and nothing more. Such agreements between entities can be made through smart contracts that outline what data can be requested and with whom that data can and cannot be shared, as well as the cost of the data.
Another potential approach to increase collaboration among CRNs is the creation of an online Data Catalog. Access to data and the value it creates is impeded by current methods used. Locating quality data for research can be extremely difficult, especially given the amount of data that exists.

---

[135] Blockchain and Artificial Intelligence. Mdepinet.net. https://www.mdepinet.net/bait. Published 2020. Accessed December 5, 2020.

[136] Landi, H. "82% Of Healthcare Organizations Have Experienced an IoT-Focused Cyberattack, Survey Finds." FierceHealthcare, 29 Aug. 2019, www.fiercehealthcare.com/tech/82-healthcare-organizations-have-experienced-iot-focused-cyber-attack-survey-finds.

[137] Ramachandran, A, and Kantarcioglu. "Using blockchain and smart contracts for secure data provenance management." arXiv preprint arXiv:1709.10000 (2017).

[138] Sharma, Toshendra Kumar. "Permissioned and Permissionless Blockchains: A Comprehensive Guide." Blockchain Certifications, 13 Nov. 2019, www.blockchain-council.org/blockchain/permissioned-and-permissionless-blockchains-a-comprehensive-guide/. Accessed January 30, 2021

A data catalog would fill this gap by using metadata from each CRN; the catalogue would provide online information about what information is stored.

AI implementation must address problems created by large amounts of data that are often located on multiple disparate nodes.[139] In traditional learning models the data is aggregated to a single node and then undergoes the training process. Large amounts (terabytes) of data must be transmitted to a node in order to perform the training of AI algorithms, requiring time and increasing security risk during transmission. Federated learning is a method that overcomes the limitation of bringing the data together at one point, working instead at distributed nodes.[140] The models trained on each node are then aggregated in order to create a final model that can be redistributed to the separate nodes. This method not only drastically cuts down the time between data transmission but removes any security concerns as well, since no personal patient information is transmitted, only model information.

Improvement in the efficacy of securing, aggregation, curation, and analysis of data is critical to the response to pandemics and emergencies, because the proposed innovations may speed the time and lower the cost of producing quality real-world evidence (RWE).

Concept Proposal

Goal:

Improve efficacy of data safety measures, real-world data (RWD) for aggregation and RWE for analysis using block chain and AI technologies.

Objectives:

- Identify CRNs that are ready for blockchain application to improve data security.
- Identify new CRNs that may benefit from starting with new tools as they build.
- Develop tools with an eye towards reusability, for use with CRNs in many clinical spaces.
- Develop a framework to evaluate the efficiency achieved by implementation of the approaches developed.

Measures of Success:

Following an evaluation framework created for this work, success can be measured by the creation of a data set that improves the safety and efficacy of CRN processes.

Methods:

A framework to evaluate innovations proposed to make CRNs more efficient should be developed to support the implementation of innovations proposed here.

The evaluation framework will build on work in the existing CRNs associated with MDEpiNet. A maturity model has been developed for CRNs that provides a context for the development of the proposed evaluation framework.[141] In addition, literature has emerged for producing a metric for return on investment and time saved by CRNs when compared to traditional methods for evidence

[139] Yang, Qiang, et al. "Federated machine learning: Concept and applications." ACM Transactions on Intelligent Systems and Technology (TIST) 10.2 (2019): 1-19.
[140] Posted on May 1, 2019 by Nick Lynch Categories: Artificial Intelligence. “Data Sharing Challenges and AI.” Pistoia Alliance, 31 Aug. 2020, www.pistoiaalliance.org/blog/datasharing_challenges__ai Accessed January 27, 2021
[141] Coordinated Registry Networks. Mdepinet.net. https://www.mdepinet.net/coordinated-registry-networks. Published 2020. Accessed December 5, 2020.

generation.[142] This evaluation framework can be developed to support many of the innovations described in this plank.

Feasibility:

The application of BC and AI are being used throughout health IT to improve efficiency, suggesting strong feasibility for use with CRN. The forthcoming BAIT White Paper describes a series of pilot projects. Currently this critical project has not been funded. This work may find support from a variety of funding agencies.

[142] Cronenwett J, Avila-Tang E, Beck A et al. Use of data from the Vascular Quality Initiative registry to support regulatory decisions yielded a high return on investment. *BMJ Surg Interv Health Technol*. 2020;2(1):e000039. doi:10.1136/bmjsit-2020-000039

Plank # 9. PREPT Pandemic Coordinating Network (PCN): Uniting Islands of Expertise

Gap Analysis

Decisions about activities of daily living that are constrained by pandemic-related risks are complex and depend on multifactorial analysis of data derived from disparate sources not heretofore aggregated for such purposes. The need to transcend organizational boundaries and promote effective healthcare delivery noted by the Healthcare Information and Management Systems Society (HIMSS) is magnified by the need to achieve syntactic and semantic interoperability across traditional ecosystem boundaries. In their letter to House and Senate leadership of July 22, 2020, HIMSS and other groups noted that lack of automated interoperable and accurate data exchange and sophisticated analytic tools impairs the ability of decision-makers to make smarter and faster decisions that could save lives during national emergencies like the current pandemic.

For example, to guide decisions that change behavior related to "normal life," not only must viral testing reach populations at risk but test-related data must be integrated with existing and emerging data relevant to activities desired by these populations to further their health, well-being and economic stability. Such activities include return to work or school and development of protected "bubbles" that permit populations at risk to interact and transact in activities of daily living as safely as possible. It is also important to detect, localize and correctly interpret early signals of flares in disease transmission or changes in access to critical resources that affect high-risk and disadvantaged communities and provide specific guidance about meaningful alterations in behaviors to mitigate these risks based on quality evidence. This proposal follows recommendations from social action theory on development of systemic coordinated networks through formation of a separate coordinating organization with visionary team leadership.[143]

As in all sectors, considerations regarding return-to-school strategies must encompass the broader implications beyond the target population. Rapid viral testing is recommended as an important component of reopening models, although such testing has not been widely applied in the educational sector.[144,145] Comprehensive testing may be especially important in young, otherwise healthy individuals in whom symptoms, including fever, are rare in those infected with and transmitting the SARS-CoV-2 virus.[146] However, the value proposition for testing school-age children is uncertain, given that where common mitigation strategies are employed it may take 25 infected children to result in one new in-school infection. Understanding these dynamics is essential to appropriately integrate testing access and response planning in the successful reopening of schools. Such issues must be integrated with many other factors to achieve substantive and relevant guidance.[147] Strong in-school mitigation strategies are critical. Community disease incidence, community commitment to and success with mitigation measures,

[143] Hage J. *Knowledge Evolution and Societal Transformation: Action Theory to Solve Adaptive Problems*. Anthem Press; 2020.

[144] Landeros A, Ji X, Lange KL, et al. An Examination of School Reopening Strategies during the SARS-CoV-2 Pandemic. *medRxiv*. Published online 2020.

[145] Rafiei Y, Mello M. The Missing Piece — SARS-CoV-2 Testing and School Reopening. *New England Journal of Medicine*. 2020;383(23):e126. doi:10.1056/nejmp2028209

[146] Letizia AG, Ramos I, Obla A, et al. SARS-CoV-2 transmission among Marine recruits during quarantine. *N Engl J Med*. Published online 2020.

[147] Panovska-Griffiths J, Kerr C, Stuart R et al. Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study. *Lancet Child Adolesc Health*. 2020;4(11):817-827. doi:10.1016/s2352-

proportions of school age children as well as elderly and other high-risk groups in the community, and community-wide test and trace strategies can all play important roles in the effect of school reopening on community transmission rates and vice versa.[148,149] In fact, the greatest aggregate risk falls on adults outside school settings. Recent data suggest that spread comes from the community to schools, and not from schools to the community. Schools do not appear to be a source of superspreader events, and interventions aimed at children are unlikely to have a substantial impact on transmission. [150,151] There are growing silos of data on COVID-19 in schools, including a multi-stakeholder effort led by Qualtrics to gather data from over 5,000 schools in 47 states, including more than 5 million students and staff.[152] School administrators, faculty and parents appreciate straightforward information that can help them make safer and more effective decisions; a difficult threshold to achieve in such a volatile environment.

There are a number of conflicting forces at play. Reopening schools increases travel and contacts outside the home for parents and families returning to more normalized activities including work. On the other hand, apparently safe and convenient strategies, like relegating students with disabilities to remote learning, may disrupt access to vital services for which these students normally rely on at-school delivery,[153] although individual cases likely need in-depth consideration and issue-specific guidance outside normal algorithms.[154,155,156] Certainly, the deleterious effects related to school closure are disproportionately magnified in low-income and underserved populations.[157] Return-to-school strategies cannot be one-dimensional. Testing, tracing, tracking, social distance and isolation must all be viewed in the holistic context of the participants, their relationships, and the communities in which they live.[158] There is a growing sense in the clinical community working with school-age children that, given use of common mitigation measures, all children are safer in school than elsewhere, although this conclusion is not universally held.

There are numerous data silos regarding COVID-19 testing, health data relevant to significant subpopulations, data about community transmission rates, data about strategic options for return to school, etc., yet there are not global strategies or guidance that incorporate data points important

[148] Goldhaber-Fiebert J, Studdert D, Mello M. School Reopenings and the Community During the COVID-19 Pandemic. *JAMA Health Forum*. 2020;1(10):e201294. doi:10.1001/jamahealthforum.2020.1294

[149] Levinson M, Cevik M, Lipsitch M. Reopening Primary Schools during the Pandemic. *New England Journal of Medicine*. 2020;383(10):981-985. doi:10.1056/nejmms2024920

[150] Boyle P. Kids, school, and COVID-19: What we know — and what we don't. AAMC. https://www.aamc.org/news-insights/kids-school-and-covid-19-what-we-know-and-what-we-don-t. Published 2020. Accessed December 5, 2020.

[151] Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med* 2020; 26(8): 1205-11.

[152] AASA. COVID-19 School Response Dashboard. Statsiq.co1.qualtrics.com. https://statsiq.co1.qualtrics.com/public-dashboard/v0/dashboard/5f78e5d4de521a001036f78e#/dashboard/5f78e5d4de521a001036f78e?pageId=Page_c0595a5e-9e70-4df2-ab0c-14860e84d36a. Published 2020. Accessed December 5, 2020.

[153] Joline EB, Lainie KH, Susan DA, Amy J H, Robert R, Maurice G. S. School reopening during COVID-19 pandemic: Considering students with disabilities. *J Pediatr Rehabil Med*. 2020;13(3):425-431. doi:10.3233/prm-200789

[154] Downes K, Danziger-Isakov L, Cousino M et al. Return to School for Pediatric Solid Organ Transplant Recipients in the United States During the Coronavirus Disease 2019 Pandemic: Expert Opinion on Key Considerations and Best Practices. *J Pediatric Infect Dis Soc*. 2020;9(5):551-563. doi:10.1093/jpids/piaa095

[155] Hamilton J, Ameel K, Asfour F. Returning to school in the midst of the COVID-19 pandemic for children with cystic fibrosis. *Pediatr Pulmonol*. 2020;55(10):2502-2503. doi:10.1002/ppul.24973

[156] Hamilton J. Returning to school in the midst of the COVID-19 pandemic for children with chronic disease and special needs. *J Pediatr Nurs*. 2020. doi:10.1016/j.pedn.2020.07.010

[157] Dooley DG, Bandealy A, Tschudy MM. Low-Income Children and Coronavirus Disease 2019 (COVID-19) in the US. *JAMA Pediatr* 2020;174:922-3.

[158] Armitage R, Nellums LB. Considering inequalities in the school closure response to COVID-19. *Lancet Glob Health* 2020;8:e644.

to decision-makers and that are responsive to a rapidly changing ecosystem. It is not altogether helpful, for example, to have data on testing options for tests that are sequestered by government, or for which there are substantive additional supply chain constrictions, or for which cost, turn-around time or other factors are not suitable to the needs of the target population. In the absence of reliable and comprehensive evidence, schools are left to make conservative estimates of risk that leave students and families without access (and schools without adequate budgeting) or estimates that are overly optimistic and risk flares of transmission. Response to community events may be wholesale and disruptive (e.g., returning to distance learning after a single event), affecting continuity of educational and social supports, and denying families consistent economic security, or may be so modulated and surveillance practices so blunted that multiple new transmission events may lead to avoidable spreading before triggering a change in practice.

Refining strategies based on data will require that multiple data sources be made interoperable through data normalization so that semantic meaning can be lifted from their elements and the aggregated data made available for analysis and modeling. A catalog of metadata from potentially useful data silos, as described in Plank #4, would assist in the process of data selection. Artificial intelligence should be used to wean sources to those few that add value toward a meaningful solution. Nimble analytics and modeling will facilitate adjustment to rapidly changing parameters. Critical stakeholders need to drive the process in order that the analysis can be trusted and implemented,[159] and the results be feasible, practical, acceptable, and tailored to the needs of each community.[160] For underserved communities and those with socioeconomic and medical risk factors, attention to privacy and security are paramount to this trust.[161,162] The information generated by these communities is essential to adequately incorporate the long-term risks of deepening social, economic, and health inequities for children into the analysis.[163] The educational community is positioned to implement scalable responses. They cultivate trust in daily relationships with families and are first line responders in adoption of health mandates. In an ecosystem with disparate political concerns there is essentially universal desire by persons of every race and class to open schools safely. Solutions developed within this use case can be scaled and translated readily to other sectors.

Consultation with community members knowledgeable about the requirements for the supported decision will be necessary to develop relevant analysis and modeling. Ultimately it will also be helpful to design feedback analysis to determine the validity of the models driving the decision support. While these features are described in application to the educational community as a use case, they are applicable across social and economic sectors as citizens attempt to behave responsibly while preserving the essential structures of society and the economy.

[159] Hoover AG, Heiger-Bernays W, Ojha S, Pennell KG. Balancing incomplete COVID-19 evidence and local priorities: risk communication and stakeholder engagement strategies for school re-opening. *Rev Environ Health* 2020.
[160] Operating schools during COVID-19: CDC's Considerations. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/schools.html. Accessed December 4, 2020.
[161] Baker C, Galemore CA, Lowrey KM. Information Sharing in the School Setting During a Public Health Emergency. *NASN Sch Nurse* 2020;35:198-202.
[162] Lyons J, Akbari A, Torabi F, et al. Understanding and responding to COVID-19 in Wales: protocol for a privacy-protecting data platform for enhanced epidemiology and evaluation of interventions. *BMJ Open* 2020;10:e043010.
[163] Armitage R, Nellums LB. Considering inequalities in the school closure response to COVID-19. *Lancet Glob Health* 2020;8:e644.

Concept Proposal

Goal:

The goal of this project is to demonstrate the feasibility and value of methodology for selection and aggregation of key data from available and emerging silos to answer questions critical to progress toward a safe, evidence-based return to normal life.

Return to school has been selected as the specific use case that highlights the need for and capabilities of this concept proposal. The plank committee anticipates pilot development in school systems that reflect the diversity of conditions, practices and variations in socioeconomic and clinical risk factors, working with groups that already have a footprint in this domain. The objective of the concept proposal is to work with key stakeholders from specific at-risk populations to identify the determinants necessary to a decision to return to or withdraw from in-person education relative to pandemic factors, to select the highest quality data elements that support those determinants, to semantically lift the meaning of those data elements and achieve sufficient interoperability to permit aggregation of and operation on those elements.

An ideal strategic model will incorporate data from viral testing, contact tracing, symptom tracking, and isolation of persons known or suspected to be infected into the decision model. It will also incorporate factors that are likely to elevate or mitigate risk of viral transmission to or by the target population, and key factors that may materially affect the health and well-being of the target population. An ideal model will on the one hand embody features that are generalizable and scalable across educational communities and that are translatable to other sector use cases, and on the other hand will be responsive to the needs of the local community, responsive to issues of disparities of care and access, and responsive to rapidly changing conditions within the ecosystem. AI tools will be used to assess the quality and added value of each source and to assist the narrowing of sources to those that contribute meaningfully toward the accuracy and predictive value of the decision support model. The data models in the selected silos will be semantically lifted and cross-mapped to assure effective interoperability and to allow aggregation across sources that permits utilization within the decision support construct.

In addition to core indicators regarding community burden and implementation of mitigation strategies recommended by CDC,[164] parameters that may influence decision-making in this use-case may include:

- COVID-19 testing (supply chain, cost, turnaround time, impact, sensitivity and specificity, source (symptomatic, asymptomatic, wastewater, etc.))
- Prevalence of COVID-19 in the community, including the asymptomatic population
- Contact tracing (internal/external, inclusive/opt-in, accessibility, completeness, time, cost)
- Symptom tracking (symptoms, access, validity, authenticity)
- Availability of local health resources, including hospital and ICU beds
- Vaccination (availability, storage, cost, time, transmission, symptom severity, persistence)
- Underlying conditions (e.g., chronic lung disease, disability, immunosuppression, diabetes, psychological conditions, cardiovascular disease, obesity)
- Measurable immune response
- Genetics/proteomics

[164] COVID-19 - School Reopening: Indicators to Inform Decision Making. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/indicators.html. Accessed December 4, 2020.

- Isolation/quarantine (cost, duration, frequency) and such other data as may contribute to the focus for decision support

Note that the need is not for an exhaustive list of data sources, only a reasonable list of accessible data sources specific to this pilot effort. One assumes that expansion following a successful pilot would anticipate a larger selection of sources relevant to a more diverse set of problems.

Measures of Success:

- Do the data models include the critical data points recognized by experts in the target domain as necessary for key decision strategies related to normalization?
- Are the critical data relevant to the target population accessible?
- Do the key stakeholders trust the data selection process and are they willing to act on the basis of the decision recommendations arising from the analysis?
- Can the necessary data aggregation be performed within acceptable parameters of cost, timeliness and data quality?

Methods:

From an architectural perspective, the siloed data necessary to achieve evidence-based, reliable and implementable decisions are currently heterogeneous and polyarchic with changing and unforeseen requirements. To transform this data into a useful structure that can support decision-making, such as closing or opening schools, it must be selected on the basis of potential to contribute meaning toward a solution through modeling. Successful models must clearly understand the limitations inherent in the questions that are addressed (initially, at least, as defined by decision-making stakeholders), the present areas of uncertainty and the factors that are likely subject to change over the period of analysis (as suggested in Plank #2).[165] Since the data needed to answer meaningful questions is not currently specified in a unified schema of semantic interoperability, selected data must be harmonized prior to aggregation and analysis.

Successful data aggregation methodology must ensure that the intended meaning of the original data elements is accurately captured, and that data provenance is maintained. This project will focus on standardizing local content to data standards where they exist, and semantically translating data between standards to eliminate any ambiguity of meaning. Data analytics must be resilient to changing and uncertain needs, must support both statistical and symbolic (AI reasoning) analysis, must support both learning and discovery, and must preserve the integrity of the data and protect individual privacy concerns. The team has access to novel storage methods, indexing schemes, and query processing techniques that scale to billions of relationships across multiple nodes. Automatic load balancing and partitioning, data compression, and fine-grained security labels will promote fast, efficient, and secure processing. The team anticipates construction of simulation tools that will assist decision-makers in consideration of the potential outcomes implicit in various intervention scenarios and under differing base assumptions. The use of federated learning methods to permit virtual data aggregation without requiring transmission to

[165] Price CP, Propp AM. A Framework for Assessing Models of the COVID-19 Pandemic to Inform Policymaking in Virginia. Santa Monica, CA: RAND Corporation; 2020:42.

a single node, using AI and blockchain methods such as described in Plank #8 may also be a useful approach to reduce time and security risks required for solutions.

Proposed partners:

- VANGUARD CRN, Inc. - Kevin M. Baskin, MD; Robert Lario, MSE, MBA, PhD Cand
- High-performance Integrated Virtual Environment (HIVE) - Vahan Simonyan, MS, PhD
- Pandemic Response Network, Duke University (PRN) - Mark Sendak, MD, MPP; Suresh Balu, MS, MBA; Faraz Yashar
- Global Health Crisis Coordination Center (ghc3) - Jeff Dunkel, BS
- National Association of Community Health Centers (NACHC) - Julia Skapik, MD, MPH
- Center for Health Policy Research and Ethics, George Mason University (CHPRE) - Alison E. Cuellar, PhD, MBA
- Chesapeake Regional Information System for Patients (CRISP) - Marc Rabner, MD, MPH
- Pasadalia, Inc. - Jack Lewin, MD
- Pandemic Response and Emergency Preparedness Task Force (PREPT)

Feasibility:

For technological support of the proposed project the team will leverage the High-performance Integrated Virtual Environment (HIVE). HIVE is a massively parallel distributed computing environment where the distributed storage library and the distributed computational powerhouse are linked seamlessly. The HIVE platform has been used extensively to perform innovative technology research and development in a variety of biomedical and healthcare IT applications, including focus on large scale data, analytics, clinical and real-world evidence; infrastructure support for registries; ontology development efforts for biomedical informatics and healthcare data standards; patient advocacy, data privacy and ownership; digital health policy; national and international harmonization consulting; R&D in artificial intelligence and modern bioinformatics approaches to support healthcare. The HIVE technology framework is aligned with FDA legacy architecture for data transport, storage, and analytics with which it shares a code base.[166,167,168,169,170,171,172] The HIVE platform is endorsed by the FDA as the only big-data platform that is Authorized to Operate (ATO) under a regulatory environment. Use of the HIVE platform will ensure support and long-term sustainability: it is supported by the federal government as a legacy system and by commercial enterprises and educational academic programs; its security model, designed for sensitive healthcare data, provides comprehensive control and auditing functionality

[166] Wilson CA, Simonyan V. FDA's Activities Supporting Regulatory Application of "Next Gen" Sequencing Technologies. *PDA J Pharm Sci Technol* 2014;68:626-30.

[167] Simonyan V, Chumakov K, Dingerdissen H, et al. High-performance integrated virtual environment (HIVE): a robust infrastructure for next-generation sequence data analysis. Database (Oxford) 2016;2016.

[168] Simonyan V, Mazumder R. High-Performance Integrated Virtual Environment (HIVE) Tools and Applications for Big Data Analysis. *Genes (Basel).* 2014;5:957-81.

[169] Simonyan V, Goecks J, Mazumder R. Biocompute Objects-A Step towards Evaluation and Validation of Biomedical Scientific Computations. *PDA J Pharm Sci Technol* 2017;71:136-46.

[170] Alterovitz G, Dean D, Goble C, et al. Enabling precision medicine via standard communication of HTS provenance, analysis, and results. PLoS Biol 2018;16:e3000099.

[171] Curbera, F., et al. "Blockchain: An enabler for healthcare and life sciences transformation." IBM Journal of Research and Development 63.2/3 (2019): 8-1.

[172] Submitting Next Generation Sequencing Data to the Division of Antiviral Products. Center for Drug Evaluation and Research (CDER), U.S. Department of Health and Human Services Food and Drug Administration, 2019. https://www.fda.gov/media/129126/download. Accessed November 12, 2020.

in compliance with HIVE's designation as a HIPAA and GDPR compliant, FISMA Moderate system. HIVE has guaranteed maturity and stability of approximately 10 years of heavy use under constant load conditions in a research and regulatory environment with all types of data; scalability evidenced with +25 petabytes of biomedical and healthcare data across 400 databases supported and millions of computational jobs every year.

By relying on this sustainable and hardened platform of innovation and its well-published features the project authors can concentrate on supporting the actual use cases using their expertise in regulatory, economic, biomedical and clinical research.

This pilot project, appropriately funded, is within the resources of the partnership group to accomplish successfully.

Plank # 10. All Payers Claims Database: A Critical Resource for Real-World Evidence Use to Combat the Pandemic

Gap Analysis

The failure of our national pandemic response involves what has been called a "tragic data gap."[173] One of the specific limitations of our current health information system is the lack of a national all payer claims database (APCD).[174] A national APCD would provide a tool for comprehensive understanding of the healthcare system that no existing data source supplies. Creation of this would be of great benefit to the national development of real-world evidence (RWE) needed as part of our response to COVID-19 and for evaluation of medical products[175] including diagnostics and vaccines. A strong health policy literature supports creation of a national APCD and its many applications.[176] Currently over 30 states either maintain or are planning an APCD.[177]

A national APCD has recently been considered as part of a larger piece of legislation out of the Senate Health, Education, Labor, and Pensions Committee, S.1895 - Lower Health Care Costs Act.[178] The purpose of its creation by Congress was to enable study of pharmaceutical prices. Support for the APCD portion of the bill has continued over the year.[179,180] Appropriate privacy safeguards and sharing with states have been planned. Issues of privacy and security of an APCD have been comprehensively addressed.[181]

[173] Schneider EC. Failing the Test — The Tragic Data Gap Undermining the U.S. Pandemic Response. *New England Journal of Medicine*. 2020;383(4):299-302. doi:10.1056/nejmp2014836

[174] Shachar C, Cohen G, Gerke S. Maximizing Use Of Claims Data To Address COVID-19: We Need To Revisit Gobeille v. Liberty Mutual: Health Affairs Blog. *Health Affairs*. https://www.healthaffairs.org/do/10.1377/hblog20200805.788636/full/. Published August 7, 2020. Accessed December 4, 2020.

[175] Young CL, Fiedler M. What can be done to improve all-payer claims databases? Brookings. https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2020/10/23/what-can-be-done-to-improve-all-payer-claims-databases/. Published October 26, 2020. Accessed December 4, 2020.

[176] Young C, Fiedler M. What Can Be Done to Improve All-Payer Claims Databases? Commonwealthfund.org. https://www.commonwealthfund.org/blog/2020/what-can-be-done-improve-all-payer-claims-databases. Published 2020. Accessed December 5, 2020.

[177] Inventory and Prioritization of Measures To Support the Growing Effort in Transparency Using All-Payer Claims Databases. Ahrq.gov. https://www.ahrq.gov/data/apcd/backgroundrpt/intro.html#uses. Published 2020. Accessed December 5, 2020.

[178] Text - S.1895 - 116th Congress (2019-2020): Lower Health Care Costs Act. Congress.gov. https://www.congress.gov/bill/116th-congress/senate-bill/1895/text. Published 2020. Accessed December 5, 2020.

[179] What Can Be Done to Improve All-Payer Claims Databases? Commonwealthfund.org. https://www.commonwealthfund.org/blog/2020/what-can-be-done-improve-all-payer-claims-databases. Published 2020. Accessed December 5, 2020.

[180] Young CL, Fiedler M. What can be done to improve all-payer claims databases? Brookings. https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2020/10/23/what-can-be-done-to-improve-all-payer-claims-databases/. Published October 26, 2020. Accessed December 4, 2020.

[181] Bureau of Health Information (BHI). "Data Matters–Linking Data to Unlock Information. The Use of Linked Data in Healthcare Performance Assessment."2015. https://www.bhi.nsw.gov.au/__data/assets/ Pdf file/0003/290712/DataMatters.pdf. Accessed December 5, 2020.

Users of APCD:

State-based APCD have been effectively used to study the cost of pharmaceuticals and facilitate measures of continuity of care and coordination of care.[182] Because of the large size of these databases, rare events and smaller entities (e.g., individual providers, small areas) can be studied. Tools for improving quality of care and population health may be used on APCD. As mentioned, they create a more comprehensive picture of outpatient and pharmacy care.[183] APCD have been used to help states develop strategic plans for public health legislation, to determine the impact of policy changes, and to conduct comparative effectiveness studies.

In cooperative agreement with the FDA, Medical Device Epidemiology Network (MDEpiNet) established Coordinated Registry Networks (CRNs) in 12 clinical areas and have used an APCD-like approach as part of a framework to evaluate medical products. As a public private partnership, MDEpiNet has developed CRNs for a variety of medical products that provide evidence to multiple stakeholders with diverse data needs.[184] CRNs link clinical specialty society registries to other data including claims, EHR, patient generated data and remote monitoring data to provide longitudinal outcomes. As an example, vascular surgeons have developed an CRN that links the national Vascular Quality Initiative (VQI) registry with the CMS database (VISION).[185] CMS data is equivalent to a national APCD for the over-65 population and provided longitudinal follow-up data when linked to a cohort of patients that receive medical devices; the resulting data set was used to evaluate those devices.[186]

Another potential use of an APCD is the evaluation of the long-term safety and efficacy of new vaccines for SARS-CoV-2. Waning of effectiveness of vaccines and adverse events that occur over time are anticipated and must be studied. The new vaccines becoming available through the Emergency Use Authorization make this need acute. The APCD could be used to follow cohorts from the original randomized clinical trials, at much lower cost compared to traditional subject tracing. The APCD could also follow large cohorts in the population that have been vaccinated for SARS-CoV-2 over time, even when insurance coverage or state residency changes. The APCD would also allow follow-up of the well-characterized cohorts of patients in specialty society registries who are vaccinated. Epidemiological and biostatistics methods have been developed to

[182] Pollack CE, Hussey PS, Rudin RS, et al. Measuring care continuity: a comparison of claims-based methods. *Med Care.* 2016;54(5):e30-4. PMCID:PMC4101051

[183] AHRQ. https://www.ahrq.gov/data/apcd/backgroundrpt/references.html. Accessed December 4, 2020.

[184] The Medical Device Epidemiology Network (MDEpiNet). Mdepinet.net. https://www.mdepinet.net/. Published 2020. Accessed December 5, 2020.

[185] MDEpiNet VISION http://mdepinet.org/wp-content/uploads/2019-VISION-Meeting-Agenda_DRAFT_8_6_19_AS_pgedits8.15.19_km.pdf Accessed December 9, 2020

[186] Pappas G, Berlin J, Avila-Tang E, et al. Determining value of Coordinated Registry Networks (CRNs): a case of transcatheter valve therapies. *BMJ Surgery, Interventions, & Health Technologies*. 2019;1(1). doi:10.1136/bmjsit-2019-000003

evaluate vaccines using real-world data (i.e., CMS data) that can guide analysis envisioned here.[187] Japan has used its national claims database to study an influenza vaccine.[188]

Concept Proposal

Goal:

Create a prototype study using a state-based all payer claims database linked to clinical subspecialty registries. These CRNs will be used to study the morbidity and mortality of COVID-19 in high risk patients and the safety and efficacy of vaccines.

Objectives:

- Demonstration of statistical methods for linking clinical specialty society registries to state APCD for vaccinations.
- Creation of a template for national study of vaccine safety and efficacy using RWE.

Methods:

States with APCD (e.g., California and New York State) should be identified for use in a proposed study. MDEpiNet has access to and extensive experience with both states' data resources.

CRN should be identified to match patients in state APCD. The Vascular Quality Initiative (VQI) and the Data Hub (DH) of the American Society for Hematology both have plans to evolve into CRN and would be excellent partners for the proposed pilot. The VQI and the DH offer patients at high risk for morbidity and mortality of COVID-19 (i.e., end stage renal disease and multiple myeloma patients). The registries would collect vaccination status of the patients and link them to claims data. This would replace traditional patient tracing to obtain longitudinal data. Patient-matching methods that have been successfully used by MDEpiNet to link Medicare claims data to a registry can be adapted to this state linkage proposal.

MDEpiNet can also explore the use of registries of vaccinated patients that are anticipated to be created as new vaccines are rolled out to the population. This exploration should focus on states that have existing APCD.

Feasibility:

MDEpiNet has successfully used state databases, is working with national specialty societies' registries, and has done linkage of the type discussed here, all of which supports the feasibility of

[187] Izurieta HS, Chillarige Y, Kelman J, et al. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017–2018. *The Journal of Infectious Diseases*. 2018;220(8):1255-1264. doi:10.1093/infdis/jiy716.

[188] Shibata N, Kimura S, Hoshino T, Takeuchi M, Urushihara H. Effectiveness of influenza vaccination for children in Japan: Four-year observational study using a large-scale claims database. *Vaccine*. 2018;36(20):2809-2815. doi:10.1016/j.vaccine.2018.03.082

this study. This concept proposal is an excellent candidate for consideration by PCORTF to expand its funding of CRN work.

VI. Appendices

Appendix A. PREPT Task Force names and affiliations

Task Force Co-Chairs:

1. Kristi Mitchell, MPH
   Practice Director, Center for Healthcare Transformation
   Avalere Health

2. Nick Tsinoremas, PhD
   Vice Provost for Research Computing and Data
   Director, Center for Computational Science
   University of Miami

3. Gregory Pappas MD, PhD
   Associate Director for National Surveillance
   OBE/CBER/FDA

Task Force Members:

1. Andrew Auerbach, MD, MPH
   Professor of Medicine in Residence
   University of California San Francisco

2. Kevin M. Baskin, MD
   Director of Interventional Radiology
   Sharon Regional Medical Center
   CEO, VANGUARD CRN

3. Elise Berliner, PhD
   Director of Health Technology Assessment
   Agency for HealthCare Research and Quality (AHRQ)

4. Nancy A Dreyer, PhD, MPH, FISPE, Fellow DIA
   Chief Scientific Officer and Senior Vice President
   Head, Center for Advanced Evidence Generation
   IQVIA Real-world Solutions

5. Jeff Dunkel, BS
   CEO of NuHope

6. Jens Eldrup-Jorgensen, MD, FACS
   Division of Vascular Surgery, Maine Medical Center
   Professor of Surgery, Tufts University School of Medicine
   Chief Medical Officer, Society for Vascular Surgery Patient Safety Organization

7. Laura Esserman, MD, MBA
   Director, Carol Franc Buck Breast Care Center
   Alfred A. de Lorimier Endowed Chair in General Surgery
   Professor of Surgery and Radiology, University of California San Francisco

8. Constantine Gatsonis, PhD
   Brown University

9. Marni Hall, PhD, MPH
   Vice President of Clinical Evidence
   IQVIA

10. Carolyn Hiller, MBA
    Program Manager
    Medical Device Innovation Consortium (MDIC)

11. Hartley LeRoy, MS
    ORISE Fellow/OCEA/CDRH/FDA

12. Jack Lewin, MD
    CEO
    National Coalition on Health Care

13. Konstantinos Makrodimitris, PhD
    OHT6/CDRH/FDA

14. Danica Marinac-Dabic, MD, PhD, MMSc, FISPE
    Associate Director, Office of Clinical Evidence and Analysis
    OCEA/CDRH/FDA

15. Dave Mandelkern, MS
    Chair
    Quantum Leap Healthcare Collaborative

16. Ross D. Martin, MD, MHA, FAMIA
    President
    360 Degree Insights LLC
    Program Director, CRISP Research Initiative
    Chesapeake Regional Information System for Our Patients (CRISP)

17. Ali H. Mokdad, PhD
    Chief Strategy Officer, Population Health
    Director, Middle Eastern Initiatives / Professor, Health Metrics Sciences
    Institute for Health Metrics and Evaluation, School of Medicine, University of Washington

18. Elizabeth Paxton, PhD
    Director, Postmarket Surveillance Program
    Kaiser Permanente

19. Art Sedrakyan, MD, PhD
    Professor at Weill Cornell Medical College
    Director - Medical Device Epidemiology Network (MDEpiNet) Coordinating, Science and Infrastructure Center

20. Murray Sheldon, MD
    Associate Director
    OST/CDRH/FDA

21. Vahan Simonyan, PhD
    MDEpiNet HIVE

22. Julia Skapik, MD
    CMIO, National Association of Community Health Centers

23. Scott Smith, PhD
    Director, Division of ASPE/HHS

24. Marta Steliac, MS
    Health Science Administrator
    OCEA/CDRH/FDA

25. James Tcheng, MD
    Professor of Medicine in the Division of Cardiology
    Professor of Informatics in the Department of Community and Family Medicine
    Duke University, Durham

26. Meena Vythilingam, MD
    Director, Center for Health Innovation, OASH/HHS

27. William A Wood, MD, MPH
    Associate Professor of Medicine, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center
    Chair, Data Hub Oversight Group, American Society of Hematology Research Collaborative

Appendix B. BAIT Task Force names and affiliations

Task Force Co-Chairs:

1. Gil Alterovitz, PhD, FACMI
   AI Director, VA

2. Vahan Simonyan, PhD
   Professor of Bioinformatics & Biostatistics, George Washington University,
   Chief Scientist, DNA-HIVE, MDEpiNet-HIVE
   Adjunct Professor, George Washington University

3. Yelena Yesha, PhD
   University Professor Department of Computer Science and Electrical Engineering
   UMBC
   Director, National Science Foundation Center for Accelerated Real Time Analytics

Task Force Members:

1. Jerry Baulier, MSc
   Vice President
   IOT R&D

2. Morgan Crafts, MBA
   Health IT Northrup Grumman
   Research & Development Portfolio, Health Protection Solutions
   Northrop Grumman Systems Corporation

3. Francisco (Paco) Curbera, PhD
   Heads Watson Health AI and blockchain initiatives
   Director, Blockchain and Consumer Health Development at IBM Watson Health

4. Pierre D'Haese, PhD
   CEO of Neurotargeting, Director of Digital Health and Analytics
   Rockefeller Neuroscience Institute

5. Joseph Drozda Jr., MD, MACC
   Director Outcomes Research
   Mercy Health

6. Scott Duvall, PhD
   Director of the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI) Health Services Research and Development
   Associate Professor in the University of Utah School of Medicine Division of Epidemiology

7. Gül Ege, PhD
   Senior Director
   SAS IoT R&D

8. Elisabeth George
   Head of Government Affairs, Standards and Regulation
   Philips Healthcare and Consumer Products

9. Wendy Henry, MS
   Specialist Leader, Deloitte Global
   Principal AI and Blockchains

10. Vasant Honavar, PhD
    Artificial Intelligence, Machine Learning, Data Science & Informatics Researcher
    Professor, and Center Director, Penn State University

11. Michaela Iorga, PhD
    Senior Security Technical Lead for Cloud Computing
    National Institute of Standards and Technology

12. Charles Kaminski
    Enterprise Architect Company

13. Rick Kuntz, MD, MSc
    Chief Medical and Scientific Officer
    Medtronic

14. Hartley LeRoy, MS
    ORISE Fellow/OCEA/CDRH/FDA

15. Patrick Lilley, PhD
    CEO
    Liquid Biosciences Statistician

16. Jeb Linton, BSEE
    Director of IBM Center for Advanced Studies Capital Area
    Principal Scientist for AI and Blockchains
    CTO, Partner Ecosystem and Cognitive Security
    IBM Cloud Native Center of Competence

17. Michael Mylrea, PhD
    Executive Director for AI and Cyber security
    Director, Cybersecurity R&D for Operational Technology |
    GE Global Research

18. Sharon-Lise Normand, PhD
    S. James Adelstein Professor of Health Care Policy
    Department of Health Care Policy, Harvard Medical School
    Department of Biostatistics, Harvard T.H. Chan School of Public Health
    Director, Medical Device Epidemiology Network (MDEpiNet) Methodology Center

19. Maria Palombini, MBA
    Heads blockchain in healthcare in IEEE
    Director, Emerging Communities & Initiatives Development, Global Business Strategy & Intelligence, IEEE Standards Association

20. Fadia T. Shaya, PhD, MPH
    Professor and Director, Data and Implementation Science
    Institute of Clinical and Translational Research
    University of Maryland Schools of Pharmacy and Medicine Baltimore

21. Eliot Siegel, MD
    Chief Radiologist for VA
    Capital Area and Vice Chair of Radiology University of Maryland Medical School