2020 Global Conference on Regulatory Science

CONFERENCE PROCEEDINGS

October 20-21, 2021
Hosted by the Harvard-MIT Center for Regulatory Science

ABOUT THE HARVARD-MIT CENTER FOR REGULATORY SCIENCE

The Harvard-MIT Center for Regulatory Science was established in 2018 to advance research and education in regulatory science. The Center serves the broad community of biomedical research scientists and physicians in academia, industry, and regulatory agencies who seek to improve the development and evaluation of medical products. The primary principle underpinning these activities is the understanding that scientific discoveries will most benefits patients if accompanied by an efficient, rigorous, and adaptable approach to evaluating the many rapidly emerging biotechnologies. The Center aims to be a platform to foster interdisciplinary and multi-stakeholder discussions on scientific and infrastructure needs. The Center supports a Regulatory Science Fellowship, local and international conferences, and a portfolio of research collaborations with regulatory agencies, industry, and other academic institutions.

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I. INTRODUCTION

What is Regulatory Science?

Rapidly evolving areas of science are promising new approaches to improving health while demanding new tools, standards, and approaches to evaluate the safety, efficacy, quality, and performance of innovative products. Regulatory science comprises a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. Effective regulatory science requires dialogue and collaboration between academic investigators active in the field, and the government and industry groups for whom the evaluation, regulation and marketing of medical products is a central concern.

Conference Context

Hosted by Harvard-MIT Center for Regulatory Science (CRS), the 2020 [Global Conference on Regulatory Science](#) was held virtually over 2 days October 20-21, 2020. The event convened academic scientists and physicians, international regulators, industry experts, and patient groups to explore emerging topics at the intersection between regulatory science and therapeutic development. This included 500+ conference participants from over 35 countries in Europe, Asia and South America as well as the United States (U.S.) and Canada.

Regulatory science comprises a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine.

The first in an annual series, the theme of the 2020 Conference was **Machine Learning and Data Science**, with an emphasis on the diverse ways in which new computational approaches are integrating preclinical and clinical trial data, real-world evidence, and information from electronic devices such as wearables to fundamentally alter the process of drug development, and therefore of medical care.

The Conference was conducted in the context of the ongoing COVID-19 pandemic. Characterized by shortages of medical supplies and devices, and need for rapid, safe development and deployment of diagnostic tests, therapeutics, and vaccines, the pandemic has starkly highlighted the role for effective and innovative regulatory science. The conference was sponsored by the Amy and Joshua Boger Fund. These Proceedings summarize the invited speakers' presentations, panel discussions, and related Question and Answer sessions. The conference also included two working groups whose deliberations and outputs are reported separately.

Conference topics included

- New data approaches, including real world data and others
- Innovative trial designs and statistical approaches
- Implementing Artificial Intelligence and Machine Learning approaches
- Patient Privacy and data rights
- Patient-centric therapeutic development

- Recreating public trust
- Virtual clinical trials
- Telemedicine and remote sensing technologies
- The importance of investing in regulatory science
- The need for a concerted approach to self-governance and evidence creation

Conference Objectives: Defining the Big Tent

Opening remarks by
Peter Sorger, Co-Director of the Harvard-MIT CRS
Laura Maliszewski, Co-Director of the Harvard-MIT

The conference organizers described the purpose and goal for the series; to bring together representatives from academic medicine and science, government and regulatory agencies, and the biotech and pharma industries, to discuss how therapeutic devices and drugs are tested, regulated and marketed. **The overarching goal is to make the process more efficient and facilitate innovation, especially for areas currently lacking sufficient numbers of new therapies.** Sorger noted that the process for novel therapeutics is particularly complex with many uncertainties, and volunteers must ultimately be willing to test them in their own bodies. This requires a continuously improving ecosystem.

These dynamics are particularly evident during the COVID-19 pandemic, which depends on a partnership of government and biotech to deliver tests and vaccine, and public trust in the system to accept vaccination once available. Finally, Sorger noted that the discipline of regulatory science is a "big tent", spanning activities from design of human trials, through the regulatory approval process, and post-approval monitoring. Therefore, an additional goal of the conference was to better define the big tent, and how to promote and fund it to sustain innovation.

*The overarching goal [of regulatory science] is to **make the process more efficient and facilitate innovation**, especially for areas currently lacking sufficient numbers of new therapies.*

The organizers also stressed the overarching desire of bringing better medicines to patients in a way that is scientifically robust, timely, and occurs at a reasonable cost to patients and taxpayers. However, biomedicine's focus on understanding the biology of diseases and therapeutic mechanisms of action is insufficient to feed what is learned from studies directly into therapeutic development and evaluation. Therefore, **a modern medicine may still be subject to an antique process**. Maliszewksi argued this is the next big gap to conquer and the focus of regulatory science. A convergent discipline,[1] regulatory science applies an engineering framework to biomedicine to develop new theories, methods and tools that represent biology in a way that is quantitative and reproducible. A robust regulatory science community would maximize the impact of the $118B annual public investment in biomedical research, and reduce the time lag in bringing new therapeutics to market. But as an impartial FDA cannot incorporate its own data or research discoveries into its scientific policy-making and practice, the burden of creating the field of regulatory science must live outside the FDA.

Developing a robust regulatory science capability requires a common sense of purpose – a goal of the 2020 Global Conference – as well as a **set of priorities and tools for achieving them**, such as dedicated funding. Workforce education and training in evaluation and research reproducibility will be needed, and a forum for policy development and debate to prioritize areas of need and allow for input from all stakeholders. The vision is large, but many components are already underway in academic and industrial laboratories and in the regulatory agencies. The 2020 Global Conference aimed to crystallize a handful of priorities to begin to chart a course toward an agile, adaptive regulatory system.

II. THE NEED TO INVEST IN REGULATORY SCIENCE AND NEW MODELS OF COLLABORATION

Bridging the Data Gap between the NCI and the FDA

Sharpless began his keynote address by arguing that the regulation of clinical cancer research and the development of new medical products for cancer care has played a critical role in the United States' progress against cancer over the past two decades. He attributes this to two main factors.

Keynote speaker: **Norman (Ned) Sharpless**, Director of the National Cancer Institute (NCI) & Former Acting Commissioner of the FDA

AN INCREASED UNDERSTANDING OF CANCER BIOLOGY

First, the research engine producing new cancer therapies and diagnostics is the most exciting current area of biomedical research. Competing R01 applications to the NCI between 2013 and 2018 increased 45.9% vs. 4.9% to all other NIH Institutes or Centers. Cancer therapeutics were also the leading source of pharma revenue over the past 20 years. An increased understanding of cancer biology has attracted new, young, innovative researchers who do not view cancer as a hopeless problem and think they can make a difference.

NEW REGULATORY APPROACHES IN CANCER SCIENCE

Second, changes in cancer science have required important adaptations to regulatory approaches. It is now understood that 'cancer', even of one organ type such as the lung, is in fact many different extremely heterogeneous things with histologic and molecularly precise subtypes. **This fractionation of cancer is giving rise to precision oncology, with profound implications for cancer clinical trials.** The paradigm of a 2-armed trial with thousands of subjects, powered to identify a 2% difference in survival, has been replaced by smaller trials targeting specific subpopulations which may identify remarkably active drugs with potential for very high response rates or even complete remission.

Large randomized efficacy-finding Phase 3 trials are increasingly impractical; it doesn't make sense to "bend" heterogeneous patients into a single trial arm.

Changes in regulatory thinking have followed. Large randomized efficacy-finding Phase 3 trials are increasingly impractical; it doesn't make sense to "bend" heterogeneous patients into a single trial arm. With extremely active drugs, it becomes almost unethical to require patients to wait to access new therapies until Phase 3 trials are completed, particularly if Phase 2 results are published. Therefore, for drugs so far past the issue of equipoise, recent approvals have occurred without large Phase 3 trials. This change is good for patients, for whom effective agents become available earlier. The pharma industry is also more likely to develop new cancer drugs, knowing that approvals can be obtained earlier.

INNOVATION AT THE FDA ONCOLOGY CENTER OF EXCELLENCE

The Oncology Center of Excellence (OCE) at the Food and Drug Administration (FDA) has been in the forefront in utilizing several expedited review pathways (e.g., fast track, accelerated approval). These processes give FDA the flexibility to accelerate medication development for unmet needs; granting approval but requiring further studies in the "real world". Real world evidence that provides results about questions and populations that could not be studied by other means is also increasingly recognized as a regulatory decision-making tool; the FDA has recently made three supplemental

approval (label expansion) rulings based on such evidence. In closing, Sharpless noted that **these new approaches are working; in 2018 alone, 54 new cancer drugs were approved, and 51 were approved in the first three quarters of 2020**, despite the additional FDA responsibilities relative to the COVID-19 pandemic.

However, challenges remain.

- The cost of finding very specific types of patients for clinical trials is significant
- The per-patient expense of doing a trial has skyrocketed, leading to very expensive drugs
- It is also harder to know if an agent works if it is approved solely based on Phase 2 trials so that extensive post-market reviews of efficacy are required.

Sharpless acknowledged the work still to be done by FDA and NCI, particularly in reducing the burden of excess costs on patients with cancer, but advocated that these problems are better than those facing conditions such as infectious diseases and neurodegeneration for which no real progress has been made. It is an exciting time for cancer regulatory science and the OCE has led the way at FDA so that innovative ways of thinking can be adopted at a broader scale.

Reflecting on Regulatory Science in a Complex World

Keynote speaker:
Margaret Hamburg, Former FDA Commissioner, Foreign Secretary, National Academy of Medicine

Hamburg reflected on the importance of data and data-driven decision-making through the lens of the FDA and COVID-19. This is a critical time for science – including regulatory science – as applications of science and data are vital to addressing challenges including the pandemic, climate change, and a range of security threats. **But although the need for science has never been greater, the compact between science and society seems badly frayed**. Denigration of science and marginalization of scientific expertise by politicians and policymakers, while not new, has reached a fevered pitch during the pandemic. Science denialism abounds with politicization of basic public health measures such as wearing a mask. The entire U.S. federal science infrastructure including agencies like the Centers for Disease Control (CDC) and the FDA are under attack and being undermined, putting people at risk and worsening the pandemic.

MAINTAINING STRONG SCIENCE IN THE FACE OF CRISIS
Regulatory science has a difficult role when confronting an emerging crisis like COVID-19 when promising drugs, vaccines, diagnostics, devices and protective gear – that may be in early stages of development and testing – must be provided for populations that need help. If products are investigational, we can't let desires to do whatever we can in the face of a pandemic divert from good science and scientific principles and real, meaningful, lasting answers. Only by studying investigational products appropriately can we bring the pandemic under control as soon as possible, and position ourselves for the most appropriate response to the next pandemic. The biomedical community's mobilization has been extraordinary across disciplines, sectors, and borders but much more urgently needs to be done.

Q&A excerpt:
(Re-)Create Public Trust

"We must **separate scientific discourse from political discourse** as soon as possible." – *Raffaela Sadun*

Public understanding of the scientific process is poor. Differences in approaches or changes with new evidence have been interpreted as you keep changing your minds - you don't know what you are doing. We need to communicate the fact that we are learning so much on a daily basis and are adapting to new data.

CRITICAL UNDERINVESTMENT IN REGULATORY SCIENCE

Hamburg noted whether in time of crisis or conventional need, meaningful progress will require advances in regulatory science to combine greater understanding of underlying mechanisms of disease and biology with new technologies and scientific advances including predictive toxicology, identification and validation of biomarkers, innovative trial design, and bioinformatics including modeling and data mining. She asserted that **regulatory science has been "dangerously underappreciated, underdeveloped and underfunded".**

Given that the estimated cumulative financial costs of the COVID-19 pandemic are approximately 90% of the annual gross domestic product of the U.S.[3], we can afford investments in regulatory science. Regulatory science could be of immediate help in:

- Collaborations between the FDA and the research community to **shape clinical trials to be as streamlined as possible** while allowing clinical questions to be asked and answered
- Supporting **scale-up of production**
- Working across borders to **align standards and approaches**, reducing duplication of effort for companies and researchers
- Supporting the **integrity of supply chains and preventing shortages** of medications and other products for COVID-19 and for routine medical needs
- Taking action against **fraudulent products and claims**

In closing, Hamburg applauded the commitment to advancing regulatory science via partnering with the FDA and building other collaborations. She also reminded attendees that to adequately deliver on the promise of science, patient preferences must remain at the center of all efforts, as the real measure of treatments and products is the extent to which they address the symptoms of the patients who use them.

"Regulatory Science": Lessons from the Pandemic

Woodcock shared lessons learned to date as she serves as Therapeutic Lead for Operation Warp Speed, working to rapidly develop products during the COVID-19 pandemic. She began her remarks by noting the general lack of understanding and uptake of regulatory science by policymakers and senior scientific leadership. Additionally, unlike the successful paradigm for funding basic science investigations, funding for regulatory science has been extremely limited and disjointed.

Keynote speaker:
Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA

NEW FUNDING MODELS NEEDED FOR REGULATORY SCIENCE

Woodcock highlighted key differences between basic scientific discovery research and regulatory science. **Unlike cutting-edge biomedical research, regulatory or evaluative science must be highly disciplined and goal-driven, with a focus on rigor and high replicability**. Development of consensus standards and methods are a large part of the regulatory science effort, but the existing 'blue sky'

individual investigator funding model is a particularly bad fit for evaluative work. As a result of these dynamics, much of the biomedical research community views the clinical trial enterprise as an adjunct to exciting discovery science, NIH funding prioritizes individual scientific inquiry, the bulk of trials are conducted by the pharmaceutical and drug industries who focus on advancing individual assets rather than on the larger picture of evaluation science, and investment in scholarly pursuit of innovative methods and in regulatory science infrastructure lags.

WEAKNESS IN THE CLINICAL TRIAL ENTERPRISE
Against this backdrop, Woodcock asserted that the COVID-19 pandemic has revealed the weaknesses of the current clinical trial enterprise. In a recent FDA survey, **only 6% of therapeutic trial arms for SARS-CoV-2 in the U.S. and worldwide were designed to yield truly actionable information.** Despite massive numbers of persons with COVID-19, many studies are having enrollment problems, and major U.S. medical centers are competing for patients. Although technically quite feasible, there is no apparatus in place to achieve timely answers to clinical questions as the standard of care evolves.

Master protocols could address these questions but uptake has been slow. Industry worries about regulatory acceptance as it is a novel method; scholarly input into method development and establishment of standards is needed. Patients want master protocols focused on their disease, but patient groups are not funded to support them. The pandemic has, however, accelerated launch or re-purposing of a number of master protocols and some – more than any other trial design – have yielded definitive data on therapeutic interventions, such as dexamethasone in the RECOVERY trial.[4]

> *Q&A excerpt:* **Build an Evidence-creation Infrastructure**
>
> *"So many small, fractured trials go on around the world and don't help people."*
> *-Janet Woodcock*
>
> We need to think about how to create an evidence-creation infrastructure instead of funding individual trials. Everybody is going to have to get out of their comfort zone and give something up. Academic trialists will have to give up some autonomy. NIH will have to modify how it gives out grants. Pharma will have to participate in trials of their assets. Funders/Congress are going to have to change their definition of 'research'.

KEY BARRIERS TO PROGRESS IN CLINICAL EVALUATION SCIENCE

1. **Funding models and infrastructure**. Thinking must shift from "fund a trial" to "fund an evidence-generating infrastructure".
2. **Incentives to collaborate**. Incentives in the current academic reward structure impede academic researchers who wish to collaborate. In general, clinical research is not as valued as basic science discovery, individual contributions are valued over collaborative efforts, and researchers often must generate funding.
3. **Medical product developers' approach to clinical evaluation**. In response to pressure to quickly produce results that meet regulatory standards, biopharmaceutical and device industries prioritize the imperatives of development and set up individual trials.
4. **Lack of standardized approaches to data capture and management**. There is a strong need to integrate data capture into pre-existing workflows and record-keeping (e.g., electronic health records [EHRs]), and utilize standardized definitions to bolster accurate, reliable data entry.
5. *Lack of a community of practice for the clinical trial enterprise*. Currently in the U.S., most people with serious diseases are not offered the opportunity to participate in a trial; many trial designs are not pragmatic.

In closing, Woodcock envisioned a path forward as familiarity with and acceptance of the idea of regulatory science is slowly established. She cited the **need to convince policymakers that an additional funding stream needs to be establish, separate from basic science funding, to support evaluative science.** Regulatory science has a clear link to public health and personal well-being and she believes that "if we build it, they will come."

Self-Regulation, Research Oversight and Governance by Scientists

While much of the conference focused on formal mechanisms for regulatory oversight, Daley focused on mechanisms by which the scientific community endeavors to regulate itself. Two examples – activities leading to the establishment of international guidelines for stem cell research, and the evolving international governance of human heritable genome editing – illustrated the extent to which precedents have been established for scientists to voluntarily forgo further work in certain technologies until they can be better evaluated. They also demonstrate the challenges when ethical considerations are not anticipated sufficiently early, or when scientist self-governing does not result in political or timely regulatory change. Daley co-chairs a National Academy of Medicine Committee[2] developing a universal set of principles for scientific self-governance. He also argued that **in addition to freedom of academic inquiry, scientists bear responsibility to participate in a shared governance model that is transparent and has independent oversight**.

> *Speaker:*
> **George Daley**, Dean, Harvard Medical School

III. NEW APPROACHES IN DATA SCIENCE AND EVIDENCE GENERATION

Panel: Data Science for Innovative Trial Designs

Panelists discussed how data science innovations and new modalities are changing trial design including:

Panelists:

Amy Abernethy, Principal Deputy Commissioner, FDA (Moderator)

Adam Palmer, Assistant Professor of Pharmacology, University of North Carolina at Chapel Hill

Helga Gardarsdottir, Associate Professor, Utreht University

Peter Mol, Professor of Drug Regulatory Science, University Medical Center Groningen

Steven Goodman, Professor of Epidemiology and Population

- **Using prior human clinical trial results** for individual drugs and formal hypothesis testing to quantify what might be expected when the drugs are used in combination, thereby making subsequent trials more likely to succeed.
- **More patient-centric trial designs**, particularly decentralized clinical trials that minimize or eliminate travel to a clinical center and rely on telehealth and/or real-time monitoring of quality of life and other outcomes that are relevant to patients. While some legal, regulatory, and practice barriers exist, these designs appear to enable patients to participate more easily and to be associated with better recruitment and retention.
- **Use of Bayesian frameworks to interpret accumulating evidence**. These approaches may be more ethical (due to the ability to hone in on subgroups), and produce answers that are easier to communicate and share.

*The underlying goal is to help decision-makers understand that the **new methods will provide robust data** that can be **trusted**.*

NEW DATA APPROACHES AND TRIAL DESIGNS

A shift in the current paradigm for post-approval evaluation was also noted. As more new approvals are based on smaller trials or single-arm trials, more after-approval data are needed to supplement the basic understanding of what the drug does with follow-up in clinical practice. This paves the way for post-licensing evidence generation from use of disease- or product-specific registries, and EHRs. The latter, generated in usual care settings, may not have data quality similar to clinical trial data, but may include more meaningful outcomes data and are improved with some data curation. Discussion ensued regarding the extent to which new data approaches and trial designs are being incorporated into regulatory decision-making.

NEXT STEPS TO IMPLEMENTATION

The concept of "regulatory familiarity" was cited. Decision-makers at FDA are trained to be conservative to protect public health and therefore designs featuring "fancy" ideas or **novel approaches such as Bayesian analysis** may be contemplated, **but must be seen in action in order to build confidence**. Additional suggestions to build regulatory confidence included "build on something we already know," bring new concepts from other fields in step-by-step, and provide examples. The underlying goal is to help decision-makers understand that the new methods will provide robust data that can be trusted. Finally, concern was expressed that FDA decision-making processes do not always allow it to learn well from its own decisions, in part because key information is buried deep in documents and rarely shared across centers or disease areas. Additional transparency is needed as to the basis of decisions, and the information must be made accessible to its own staff.

Data Science in Biomedical Research & Development: *Opportunities, Challenges, and Regulatory Considerations*

Speaker:
Sean Khozin, *Global Head of Data Science Innovation, Janssen*

Per Khozin, data science is novel solutions enabling a systems approach to biomedical research and therapeutic development (R&D). This is different conceptually and pragmatically from the traditional paradigm where drug development and biomedical research are distinct from health care delivery, and conducted in sequential pre-clinical, clinical and post-market stages. Rather, **with a data science approach to R&D, the system is non-linear and the phases are seamless**.[11] At the micro, or 'systems biology' level, data are leveraged from in vivo, in vitro, and clinical pipelines to better understand biologic systems, informing early development decisions.

LEARNING HEALTH SYSTEMS
Similarly, the learning health system (LHS) blurs the line between traditional clinical trials and health care delivery. Data from omics pipelines, EHRs, and digital health devices support discoveries. A LHS can extend the reach of clinical investigations to the point of care--where the majority of patients are under active monitoring and treatment--increasing recruitment and reaching underserved populations who typically don't have access to clinical trials. At the macro level, application of data science and advanced analytics to R&D programs enables use of network analysis and game theory to guide development decisions and optimize use of public and private investments for maximal societal impact.

Data science is novel solutions enabling a systems approach to biomedical research and therapeutic development

APPLYING DATA SCIENCE TO BIOMEDICAL RESEARCH AND DEVELOPMENT
Khozin summarized three overlapping data science themes in R&D:
- **External data assets**; real-world data (e.g., EHRs and mobile devices) external to that collected by traditional trials.[12] Real-world data are important to address a growing external validity deficit in traditional clinical trials.
- **The need for better data platforms**. Computation and storage considerations include providing the security features required for privacy-preserving protocols, accommodating quantum computing, and sufficient data liquidity to take advantage of decision science solutions. Platforms also need to support efficient remote data collection directly from patients participating in decentralized trials.
- **Myriad uses for novel advanced analytics** (including AI and ML) such as developing predictions from measurements from continuous systems (e.g., wearables), using AI to derive new de novo features that we cannot see (e.g., on a CT scan), or using smart analytics to develop clinically meaningful endpoints to assess safety and efficacy of therapeutics.

In conclusion, Khozin touched briefly on several regulatory considerations, including careful study design and choice of endpoints for real-world evidence generation, standard requirements for platforms, and the risks that bias can propagate more quickly in algorithms than in patient care.

Leveraging Patient-Centered Health Data Sharing Platforms for Medical Product Evaluation

> *Speaker:*
> **Nilay Shah**, Professor of Health Services Research, Mayo Clinic

Shah is working to achieve higher quality, regulatory-grade real world data that would support real world evidence or other aspects of regulatory decision-making. A particular challenge is that data sources that may be appropriate for real world evidence exist in silos, including health systems with differing EHRs, pharmacy drug databases, health insurance plan data, patient-reported outcome (PRO) measures collected by wellness programs, socioeconomic information in employment data, and sensor-based data in wearables or apps. Shah shared results and learnings from a study to test the feasibility of using a patient-centered health-data-sharing platform to obtain and aggregate health data from multiple sources.[13]

In a prospective cohort study of patients undergoing atrial fibrillation ablation or bariatric surgery (n=60), EHR data from the primary hospital and 10 additional health systems was successfully obtained and aggregated with commercial pharmacy data, digital device data from personal activity monitors, digital weight scales, and ECGs, and PRO data obtained through surveys. **Patients utilized the Hugo Health Platform which allows them to link their data from many sources into one spot, and then choose to share it with others (e.g., the research team)**. A number of benefits were identified to this approach to collecting real world data, including that patients owned their own data and could decide when and with whom to share, different identifiers (e.g., hospital medical record number and insurance company claim number) were eliminated as the patient linked all of their own data, data was in near real-time and comprehensive, the platform was used to share data back with patients, and monitoring was possible at the level of the study overall (e.g., enrollment progression, survey response rates). Challenges included time (avg=70 mins) to enroll, and the need for manual synchronization of some wearables. One patient had insufficient memory in their cell phone to participate.

IV. PATIENT-CENTRIC APPROACHES TO THERAPEUTIC DEVELOPMENT

Panel: Advances in Digital Medicine and Patient Care

Digital health is defined as all technologies at the intersection of software and health. Digital medicine is the subset of digital health with: 1) an evidence base of effectiveness, and 2) tools with the ability to interact with the healthcare sector.

> *Panelists:*
> **Ariel Stern**, Associate Professor, Harvard Business School (Moderator)
>
> **Andrea Coravos**, Co-founder and CEO, Elektra Labs
>
> **Ray Dorsey**, Director, Center for Health & Technology, University of Rochester
>
> **Luca Foschini**, Chief Data Scientist, Evidation Health
>
> **Timo Minssen**, Professor and Director of the Center for Biomedical Innovation Law, University of Copenhagen Health

DECENTRALIZED DIGITAL MODELS: TELEHEALTH & SENSORS

In opening, the panel discussed what the rapid adoption of telemedicine during the pandemic might mean for future clinical research. It was noted **that many more patients and clinicians are now getting used to telemedicine and patients, who love it, will be very reluctant to give it up**. Powerful forces may object (e.g., hospitals who cannot charge facility fees), but it will be very hard for insurers to move away from telemedicine. The shift will also translate to research, particularly as potential study subjects with conditions like cancer or ALS are at greater risk for COVID-19 and prefer not to travel. They will drive additional adoption of decentralized strategies which should result in huge cost savings, and time savings via being able to recruit a larger pool of research participants than currently.

The panel reflected on a question regarding the similarities and differences in use of remote patient monitoring in care delivery, public health, and research. It was noted that many early telehealth visits during the pandemic were people requesting tests for COVID-19; for such an urgent reason, sensors don't make sense. **Sensors and remote measuring are more appropriate for chronic** illness when something is monitored over time. It is also important to have a reason to do so, as **people who measure themselves without a clinical reason can have higher rates of depression and anxiety.** Collecting meaningful measures in studies can also be very powerful, especially in preventative care or early detection.

Q&A excerpt: **Protect Privacy**

"Dense, behavioral data over time should be thought of as private as DNA." - Luca Foschini

It is a big misconception that data from sensors is not as identifiable as genetics or other types of protected health information. It is highly identifiable by matching small 'breadcrumbs' of data over time, and it is going to be controversial as to how it will be used.

BALANCING MACHINE LEARNING INNOVATION AND PATIENT RIGHTS

Given tradeoffs between privacy and personalization with digital data, the discussants reflected on applying machine learning (ML) in this setting. The continuous nature of digital data (e.g., biometrics, symptom tracking) allows comparison to your own past, rather than to others' data, such that some self-selected experiments can be conducted with no breach of privacy concerns. Research still requires comparing data from multiple people but federated learning models can help build machine learning techniques to learn from a population while obtaining the minimal amount of information required from individuals.

Privacy is the foundation of the trust which is necessary to do longitudinal studies, and therefore is the most important consideration as research, care, and public health solutions are developed.

> **KEY SECURITY CONSIDERATIONS AROUND DATA PRIVACY**
> 1. **Focus on "data rights" rather than "data privacy"**; depending on the circumstances, a patient may or may not want privacy and may actually want their data shared. Trust comes from maintaining privacy when it is wanted.
> 2. **Data rights and security are different**. Security is an unauthorized attack on a system. Data rights/privacy is about discrimination – people don't want to be treated differently.
> 3. **Maintain trust and transparency**. As decisions are made automatically, concern arises about "black box" algorithms treating people differently, and therefore they require more ways to ensure trust and rights of individuals are maintained.
> 4. **Assess benefit & risk of tool**s. The focus for algorithms and digital tools should be on making sure the benefit outweighs the risk.

Extending the discussions to topics relevant to European Union regulations, the participants considered how ethics and privacy by design can be achieved in Europe in a way that is compliant with the General Data Protection Regulation (GDPR) in the context of digital medicine. It was noted that the GDPR sets a high bar and it could be argued whether it is realistic. **Privacy by design** (where privacy is considered from initial conceptualization of a process involving data and throughout the lifecycle) **and privacy by default** (where default settings are always the most privacy-friendly), **have been implicit requirements of data protection legislation, but GDPR embeds them in the law** in 7 key principles.[5] It is important that technologists and lawyers talk early about these issues rather than late.

AI, E-consent and Virtual Clinical Trials: Impact on Health Disparities

Speaker:
Fadia Shaya, Professor, University of Maryland School of Pharmacy

Shaya noted that currently, clinical trials, especially for COVID-19, are struggling, with the majority of trials achieving insufficient enrollment, yielding costly drug development cycles. Overall trial execution has slowed despite less time spent in regulatory phases. Significant disparities also exist in drug and vaccine trial enrollment for Black and Latinx persons vs. White. Artificial intelligence (AI) approaches may serve as both a problem and potential solution.[6] **AI and machine learning models amplify the patterns they see in inputted data, potentially exacerbating pre-existing disparities**. However, AI may also contribute to clinical trial efficiencies,[7] speeding identification of eligible subjects, analyzing complex data sets, and integrating data from disparate sources.

Shaya also reviewed promising aspects of virtual clinical trials (VCTs) for advancing increased participation in trials.[8] As most participants live far from study centers, **VCTs can improve equity and access and may improve disparities**. They should also reduce mobility and scheduling constraints that may limit study participation by certain

Q&A excerpt: **Minimize Disparities**

"Decentralization is not a nail for every hammer. Entities that can leverage the benefits in hybrid models will likely reap the benefits." - Sean Khozin

AI approaches may reduce disparities in finding cohorts of eligible patients or may exacerbate bias depending on the selection and training of the human teams developing AI. Virtual clinical trials and other decentralized approaches reduce geographic disparities and potentially those for racial and ethnic minorities. If trials are to be inclusive of underprivileged people, they need to be able to access digital tools and devices they have never had.

populations. Identification and recruitment by mining clinical data with AI techniques can quickly ensure proper demographics among participants and avoid discriminatory VCT inclusion criteria like access to broadband and ownership of a device. Finally, electronic informed consent (e-consent), while not new, has become more prevalent with pandemic-related social distancing. E-consent pilot testing should consider a range of stakeholder needs, including those of the elderly and with disabilities.

Panel: The Science and Technology of Patient Input

In opening, the panel discussed what changes in telemedicine and other remote technologies may persist, given rapid growth during COVID-19. Although telemedicine allows for a quick check-in, it is also important to determine how to enable "high touch moments" when a patient needs to see someone in the same room. To ensure patients' safety in the context of COVID-19 pandemic, healthcare teams are more open to consider data from wearable devices in addition to readings from implanted devices. It was noted that **reports of patients suffering debilitating illness or dying from deferred care because of fears of contracting COVID-19 are a microcosm of the importance of the effects of patient perspective on public health.** Patient reactions to the options available to them are far beyond what we usually look at when evaluating therapies.

> *Panelists:*
> **Annie Saha**, Director, Partnerships to Advance Innovation and Regulatory Science, FDA CDRH (Moderator)
>
> **Leslie Wilson**, Professor of Health Policy and Economics, UCSF
>
> **Barry Liden**, VP of Patient Engagement, Edwards Lifesciences
>
> **Heidi Dohse**, President and Founder, Tour de Heart
>
> **Joseph Ross**, Professor of Medicine and Public Health, Yale

Q&A excerpt: **Engage Patients**

"The common denominator is patients. Use their energy, data, and perspectives going forward."
– Barry Liden

Patients are more empowered and have access to more information than ever before. The next decade will have a significant impact on how patients are engaged in research and output. If patients are going to have trust in the system, they need to have enforceable rights. Have patients own their own data and choose how to share it. Send them results back at the end of the study. Identify benefits and risks in patient terms.

PATIENT DATA AND PATIENT PREFERENCE
In response to a question about what has or hasn't worked well relative to patient ability to access or generate their own data, panelists pointed out that data from wearable devices are providing patients with real time insights into their health and allowing them to feel safe and confident. It was noted that although more data is being collected, not all is being used appropriately. **Evidence from clinical trials focuses on outcomes like mortality or morbidity but patients want to know things like 'Will it make my symptoms better?'** Leveraging data from technologies such as wearables will help patients make better decisions. Prior research on patient preferences shows that patients may care more about avoiding risks than gaining benefits.

DIVERSITY & EQUITY IN PATIENT REPRESENTATION
The panel also considered issues of diversity and equity and how to ensure the perspectives of a broad range of patients. One idea was to include patient voices in product development and design processes, and to increase the size and number of patient profiles. However, this approach might raise concerns from the product maker community about looking at smaller subgroups with heterogeneity of preferences, as the FDA may say the product applies to only a small segment of the market, thereby limiting return on investment. The group identified a potential role for researchers to determine and provide patient preference information for different groups of patients (e.g., children, elderly, small people/big

people, differing ethnic groups) to help inform product developers. Of note, minorities and elders are underrepresented in clinical trials that support FDA approval as well as in post-marketing surveillance. **Big data has an opportunity to help by identifying patients outside the "typical" and developing clusters around characteristics.** The group concluded that manufacturers need to adjust current development and business models and focus on patient-centric therapeutics development.

V. LESSONS FROM THE COVID-19 PANDEMIC

COVID-19 in Iceland: Lessons Learned

Speaker:
Kari Stefansson, Founder and CEO, deCODE genetics

In sharing experiences of the pandemic in Iceland, Stefansson noted that the first COVID-19 case was diagnosed in February 2020; population-based screening began in mid-March. Initial mitigation measures included closing the borders, bars, restaurants and theatres, social distancing, and active contact tracing teams. Child care centers remained open. **Sequencing of the virus was undertaken for everyone identified as infected, allowing creation of a molecular epidemiology of the first pandemic wave.**[9]

Random mutations which developed into region-specific haplotypes were identified; most infections arose initially from the ski areas of Austria and Italy. Eventually, enormous sequence diversity was identified as infections spread from multiple other countries. Once containment measures were implemented, the viral transmission route changed from abroad, to people within society, to within families. Children were substantially less likely to be infected than adults, and the probability of a child transmitting COVID-19 to another person was ~half that of an adult. In the first wave 'growth phase', viral load was high with rapid accumulation of mutations. In the 'containment phase', viral load was much lower and mutation accumulations slowed. Subsequent screening and viral sequencing of 30k Icelanders revealed that antibody levels rose for 2 months and remained stable for an additional 4 months.[10] In mid-May, borders were reopened with SARS-CoV-2 PCR screening. Gradually, however, cases have mounted (including one large outbreak with a haplotype probably originating in Greece) and as of the conference, Iceland was again trying to contain a COVID-19 wave. Stefansson stressed the benefits of sequencing viral genomes with connections with contract tracing data to shed a new light on pandemic: mutations in the viral genome can be used as a "barcode" to track the spread of the virus, including direction of transmission, providing valuable information for contact tracing teams.

> *…mutations in the [COVID-19] **viral genome can be used as a "barcode" to track the spread of the virus**, including direction of transmission*

The Regulatory Response to COVID-19 in APEC: Perspectives from Singapore

Speaker:
John Lim, Executive Director, Centre of Regulatory Excellence, Duke-NUS Medical

Lim reported that Singapore's first reported COVID-19 case was identified January 23, 2020. Well-contained until early April, a surge was then identified from returning Singaporeans and cases in migrant worker dormitories. Therefore, a nationwide "Circuit Breaker" - border closure, stringent contact tracing, safe (social) distancing, mandatory mask wearing, and restrictions on gatherings and group sizes - was instituted to pre-empt local transmission. A phased re-opening began in June, and **as of September, the situation had stabilized with low community and worker dormitory spread, and mortality <0.05% (27 total deaths)**.

Measures contributing to Singapore's ability to manage the pandemic include a
- **Whole-of-government approach**. strong government leadership makes policies based on facts and science. The rationale for decisions is communicated transparently and updated with new evidence. Action is anticipatory and agile. Legislative and policy levers are aligned and received budgetary support.

- **Singapore's robust health system**, which incorporated lessons learned from the 2003 SARS outbreak. Infrastructure includes a National Center for Infectious Diseases, contact tracking via mobile apps, aggressive testing, and a pre-existing telemedicine system.
- **Regulatory agility**. Health Systems Authority (HSA) Provisional Authorization mechanisms allowed for swift emergency authorization of COVID-19 diagnostic kits and respiratory devices. HAS also has the ability to conduct first-in-world evaluation or to reference approvals elsewhere, shortening evaluation timelines.
- **Effective partnerships**. Finally, Singapore and HSA participate in partnerships and collaborations including WHO.

In conclusion, Lim cited the need for regulatory agility and coordination among national regulatory authorities for expeditious evaluation of new health products, as well as sound post-market monitoring; requirements that are more critical with the rapid pace of innovation in COVID-19 vaccines, therapeutics and diagnostics. Maintaining public trust in new vaccines must be based on robust, science-based regulatory decision-making, and transparent and ongoing communication to the lay public.

Panel: Regulatory Response to Emerging Infectious Diseases & Healthcare Crises

Panelist comments were offered in the context of unprecedented scrutiny of the FDA's regulatory processes by scientists and the public in the midst of the ongoing COVID-19 pandemic. They noted challenges, things that have gone well, and learnings that could inform improvements moving forward. Pre-pandemic, billions of dollars had been appropriated to preparedness.

Panelists:

Florence Bourgeois, Associate Professor of Pediatrics, Harvard Medical School & Co-Director, Harvard-MIT CRS (Moderator)

Steven Galson, Senior Vice President, Amgen

Meredith Buxton, CEO, Global Coalition for Adaptive Research

Paul Beninger, Director, MD/MBA Program, Tufts University School of Medicine

Raffaella Sadun, Professor, Harvard Business School

A FAILURE TO PLAN

Planning exercises correctly recognized there would be a need for vaccines, medical countermeasures, and identified mechanisms (e.g., emergency use authorizations). **Gaps in responses have resulted from a failure to imagine the scope of the crisis.** The extent of global economic disruption (and consequences on health), political polarization and vitriol and politicization of governmental organizations, and stresses on state health departments from cutbacks due to loss of state tax revenue were not anticipated. Relinquishment of leadership at the national level left states and local actors scrambling for resources (e.g., PPE), trying to fill the void. Bright spots have also emerged. Clinical trials have pivoted to assess potential COVID-19 therapeutics via innovative designs, including complex platform trials. Hospitals and healthcare systems have undergone rapid large process innovations to change their basic operations and respond to the pandemic. There has been a dramatic increase in collaboration between FDA, CDC, academia and industry in vaccine development and in assessing potential therapeutics.

*The current COVID-19 pandemic is another revelation to ask '**Why can't we do some things differently?**'*

Parallels were drawn between the regulatory decision-making during COVID-19 pandemic and other non-pandemic emergencies. In the early days of the HIV epidemic, with no treatments available, federal and institutional responses were fractured and characterized by uncertainty. AIDS patients and activists challenged the FDA about the pace of drug development and asked numbers of good questions. **Over time, a cascade of regulatory innovations – including shortening review times and using new criteria such as surrogate markers and biomarkers as endpoints – were developed to be more responsive to the population.** People were thinking in more innovative ways; a trend that continued in substantial pieces of legislation after the 9/11 disaster.

RECOVERY, TRUST, AND NEXT STEPS

The current COVID-19 pandemic is another revelation to ask 'Why can't we do some things differently?' These conversations are happening in the context of loss of public trust, including around the evidentiary requirements for approval of a vaccine developed at 'warp speed'. Pre-COVID vaccine hesitancy has been exacerbated, and must be addressed using evidence-based principles of communication and by new strong leadership heading federal institutions. The FDA must be transparent about approval standards and their processes and timelines for vaccine approvals.

Finally, panelists considered factors that will be needed to successfully and rapidly deploy and integrate novel therapies. Lessons from patients and activists include:

- Speaking out on the integrity of decision-making and regulatory processes
- Reaching out to others to personalize rather than demonize
- Addressing the value systems of affected persons.

The FDA must continue to adapt to new trial designs and models (e.g., federated approaches) to further increase efficiencies. **Some templates for cross-agency collaboration exist, but more are needed.** All stakeholders should assist in efforts to communicate the components of drug and vaccine approval in modern ways (including social media) to improve transparency and reestablish public trust. Process knowledge must also penetrate more deeply into academic institutions. In particular, medical schools and medical training play an important role as doctors are asked to improve their skills as communicators, collaborators and innovators. Physicians and scientists must also become more involved in the political system.

VI. WORKING GROUP SUMMARY
Education in Regulatory Science

Speakers:
Caleb Alexander, Professor, John Hopkins Bloomberg School of Public Health

Michael Rosenblatt, Chief Medical Officer, Flagship Pioneering

The impetus for the Working Group was rapid translational science advances that are driving new therapeutic modalities such as living cells, parts of cells (e.g., exosomes, mitochondria) on their way to being drugs, RNA, neuroprosthetics, microbiome "bugs (bacteria) as drugs", and digital therapeutics. **Those involved in regulatory science and regulators must stay up-to-date with these advances, lest a situation arise where there is sufficient specialization that the inventor may know much more about field than the regulator**.

This Working Group planned to discuss how to ensure that key people involved in the regulatory science workforce, including at the FDA and other stakeholders, are broadly trained and informed and maintain currency. Questions that may be considered include: What are the principle means currently used to train individuals in regulatory science? What core competencies should be reinforced through regulatory science education? Is there an art as well as science of regulation and how can it best be imbued? How can initiatives stay 'up to speed' with technologic advances? What strategies can maximize and incorporate experiences and views of diverse stakeholders?

Q&A excerpt: **Engage Students and Fellows**

"It is students and fellows that drive progress." -Peter Sorger

The new generation of graduate students make up the driving aspect of the regulatory science community and keep us modern in terms of what is important. In particular, there is a lot of interest in technology by trainees. We need to define the field to attract more of them, engage with learners to do projects, and fund their work.

Digital Pathology, AI and Image-Based Biomarkers in Research and Clinical Practice

Speaker:
Sandro Santagata, Associate Professor in Pathology, Brigham and Women's Hospital

Anatomic pathology is a central pillar of diagnosis in medicine; every cancer diagnosis requires evaluating a tissue specimen from a patient. The pathologist places tumors into a classification system – a taxonomy – and renders a diagnosis that intrinsically includes prognostic information. With the advent of a 2016 update to the international taxonomy, many tumor categories now require histologic and phenotypic and specific genomic information, including the presence or absence of certain mutations. Inclusion of this information has been transformative for diagnostic excellence. **Pathology is now at the cusp of a revolution in diagnosis driven by new tools and processes in the field of digital pathology**. After hearing about two potential digital pathology use cases – use of AI in analyzing stained sections, and multiplex tissue imaging to characterize markers found on immune cells – the Working Group planned to examine a range of topics including computational and imaging technologies including ML/AI algorithms, standardization of formats in research and public image repositories, image-based biomarkers, evaluation and regulatory of digital pathology as a clinical service and companion diagnostic, and challenges and needs for the field as it grows.

VII. SUMMARY AND NEXT STEPS

Summary

Drug discovery and science have historically been rewarded as "best" activities in industry and academia, while the science of evaluation (regulatory science) has been easily ignored as something best left to regulatory affairs specialists. However, new science is driving major innovations in clinical trials and diverse digital data, and the COVID-19 pandemic is causing dramatic changes in healthcare delivery, and vaccine and therapeutics development. Therefore, regulatory science is becoming a place for new statistical approaches, machine learning, and innovative advances that will directly impact how safe and effective therapeutics are made and approved.

> *Closing remarks by*
> **Florence Bourgeois**, Co-Director of the Harvard-MIT CRS
> **Peter Sorger**, Co-Director of the Harvard-MIT CRS

Recurrent conference topics included:

- Scientific discovery directly impacts the need for innovation in product evaluation – and new products require new approaches to regulation
- Trust, privacy (data rights), and patient engagement

- Reproducibility and transparency in digital algorithms and diagnostics
- Better access to trusted data sources. In particular, the issue of trust underlies many others.

Next Steps

The promises and complexities of health data integration have a technology component, but the fundamental challenge is one of trust. Developing and introducing new medicines requires consent of the governed and trust in the underlying review and regulatory process. In using digital data for real world evidence, security, privacy, and trust are as important as technical innovation. And the ongoing COVID-19 pandemic is revealing a problem with trust in biomedicine, and the pharmaceutical industry in particular. Sorger emphasized that not all regulation rests on the shoulders of government; scientists must themselves refrain from engaging in certain technologies and practices until they are better evaluated and larger societal consensus is reached about benefits and costs.

> **KEY DIRECTIONS AND REQUIREMENTS FOR BUILDING & SUSTAINING A REGULATORY SCIENCES COMMUNITY:**
> 1) Work to define a set of priorities via ongoing dialogue
> 2) Promote education and engage graduate and medical students
> 3) Conduct research into new technologies and testing protocols including machine-learning and AI applications/digital medicine
> 4) Develop neutral forums in which to consider and debate policy
> 5) Develop a stable source of funding and support for research, outreach, and training

The conference organizers challenged attendees to stay engaged whilst committing to fact-based scholarship, and to speak out in support of science-based regulation and equitable access to medicine and resources.

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