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Clinical Trials—Lessons Learned from the Pandemic

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Regulatory | Litigation | Transactional

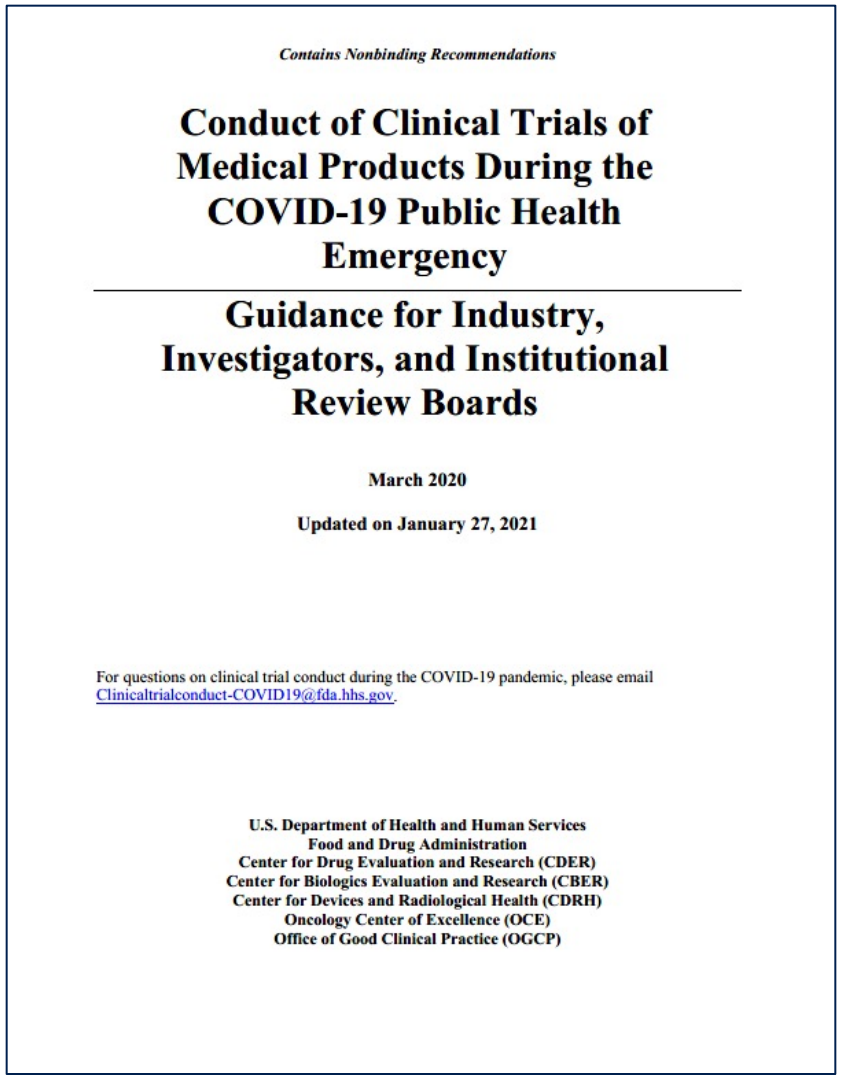
Agenda

- FDA Regulatory Considerations
- Clinical Trial Agreements and Related Documents
- Privacy and Cyber Considerations
- Questions & Answers

FDA Regulatory Considerations

FDA and Clinical Trials During the COVID-19 Pandemic

- Management of COVID-related protocol deviations and amendments
- Obtaining informed consent
- Virtual clinical trial visits
- Home delivery and/or administration of investigational product
- Use of commercial product for study drug
- Use of alternative laboratories and imaging centers
- Remote clinical outcome assessments
- Addressing delays in monitoring due to COVID



Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

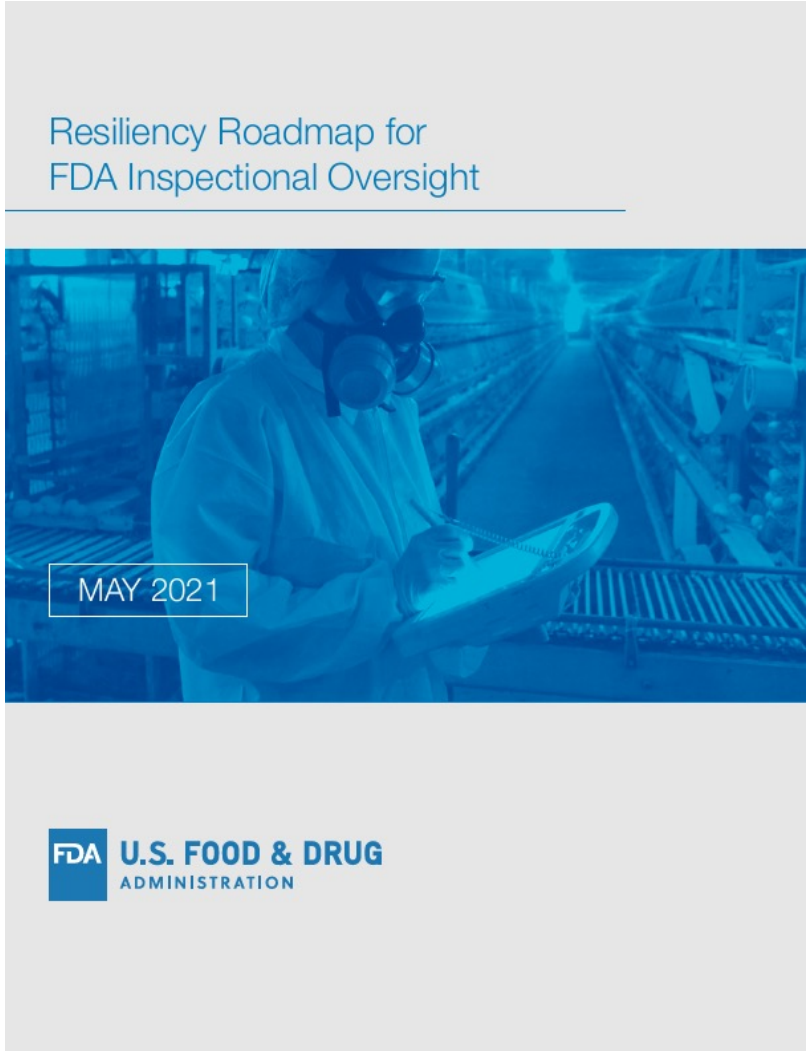
Updated on January 27, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

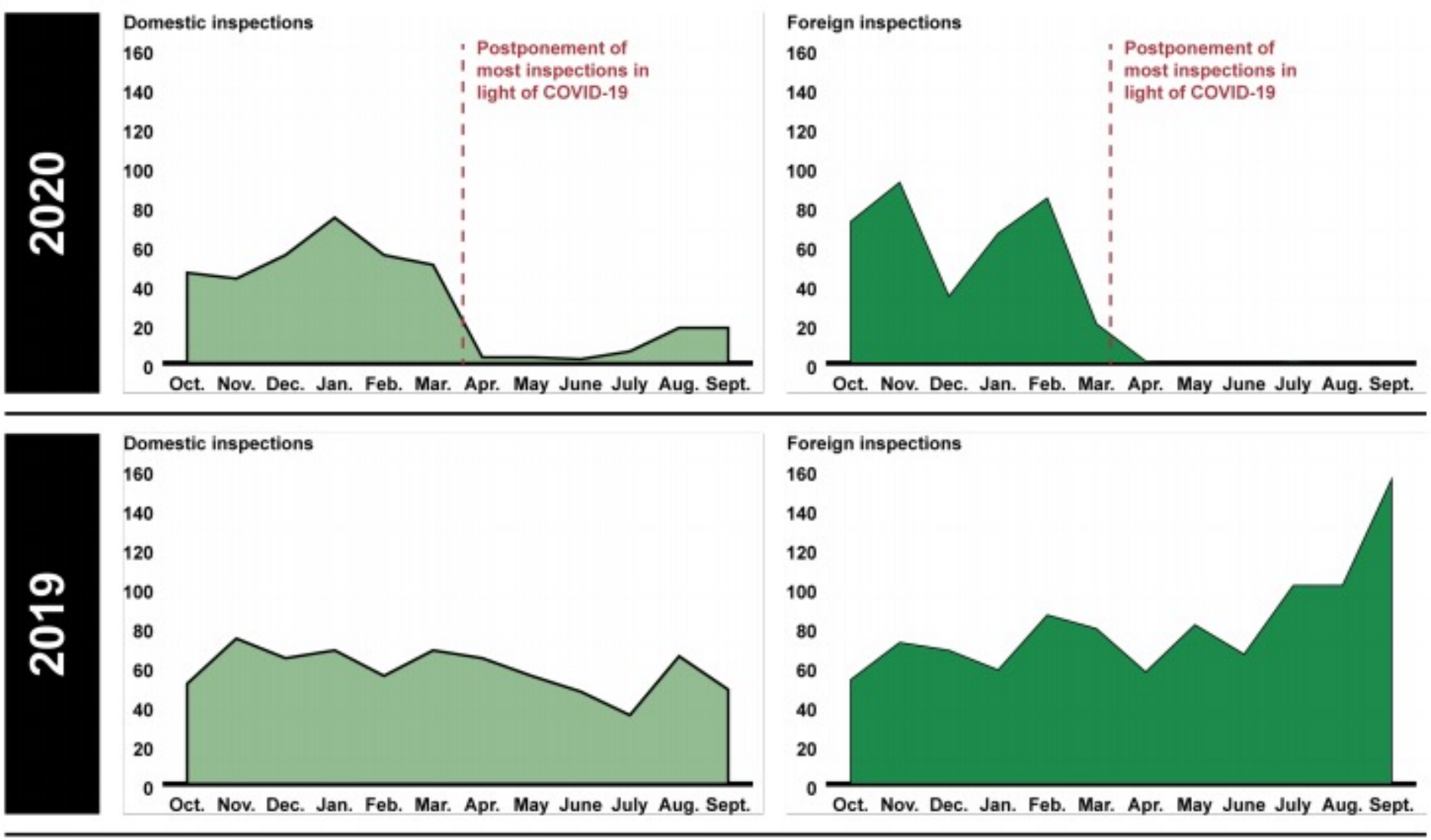
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

Bioresearch Monitoring (BIMO) Inspections

- In March 2020, FDA suspended most of its inspection program and limited inspections to those that were priority or mission-critical, including some pre-approval inspections for vaccines, important therapies and some for-cause inspections
  - Although under pressure, FDA did not embrace real-time video assessments, in which FDA investigators would examine facilities and interview employees using a live video feed
- FDA did increase its use of some alternatives to in-person inspections, such as relying on inspections by foreign regulators and requesting records in lieu of inspection
- On May 4, 2021, FDA published a "Resiliency Roadmap for FDA Inspectional Oversight" detailing its plan and priorities for inspectional oversight, including the backlog of inspections

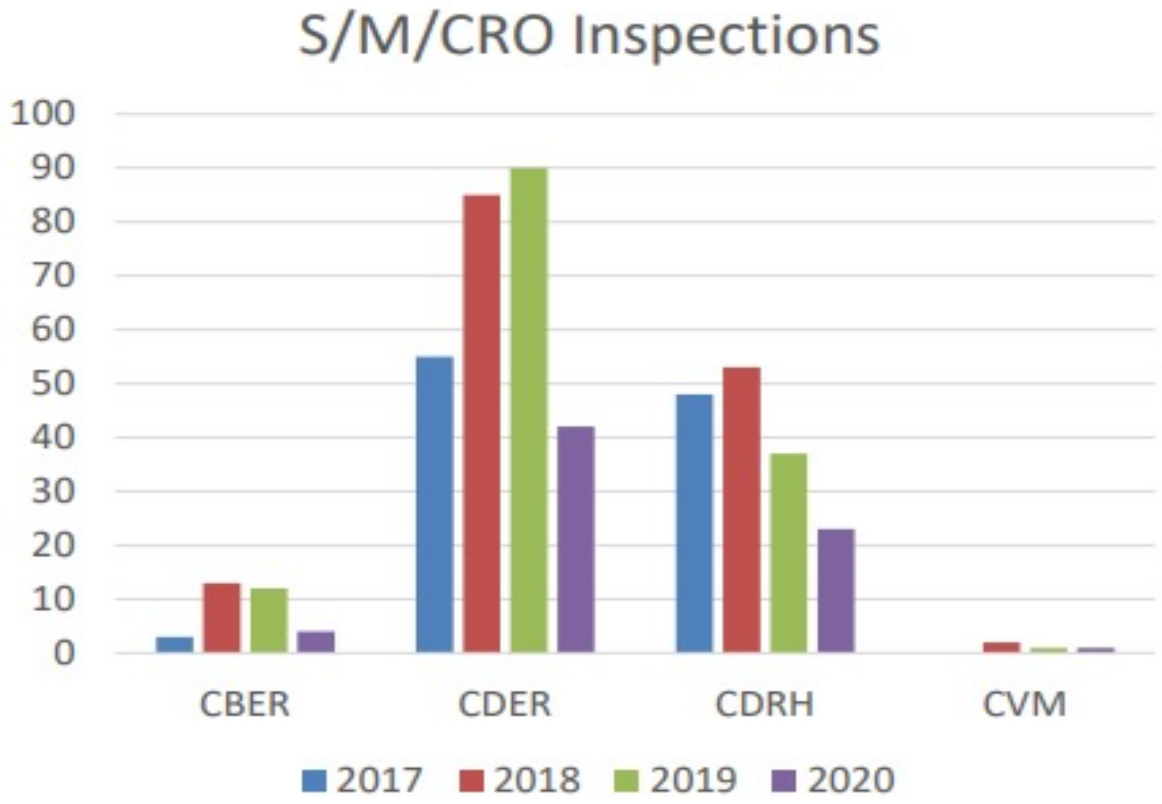


Inspections FY 2019 Versus FY 2020



Source: GAO
https://www.gao.gov/assets/gao-21

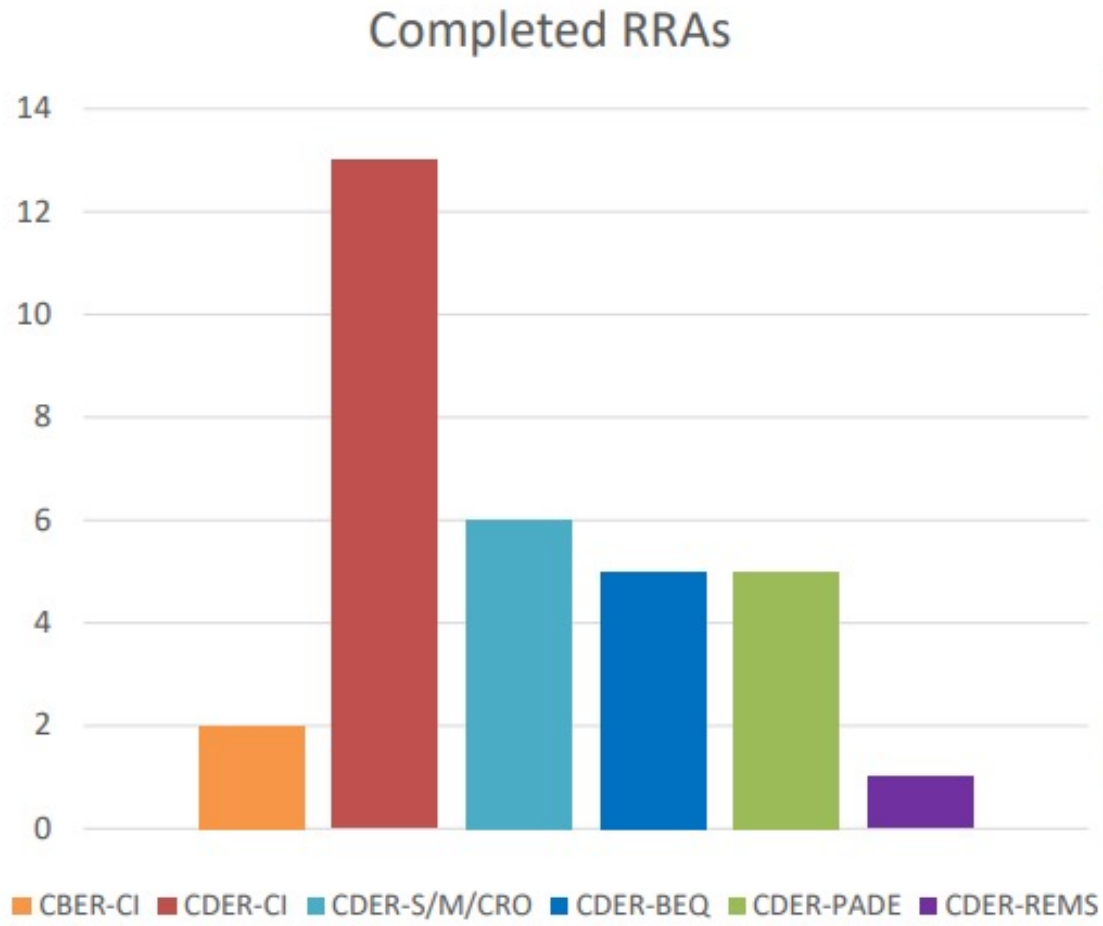
BIMO Sponsor/Monitor/CRO Inspections



Center	2017	2018	2019	2020*
CBER	3	13	12	4
CDER	55	85	90	42
CDRH	48	53	37	23
CVM	0	2	1	1

Source: FDA https://www.fda.gov/media/145858/download

“Remote Regulatory Assessments”



Center	Program area	2020
CBER	Clinical Investigator	2
CDER	Clinical Investigator	13
CDER	Sponsor/Monitor/Contract Research Organization	6
CDER	Bioavailability/Bioequivalence	5
CDER	Postmarketing Adverse Drug Experience	5
CDER	Risk Evaluation Mitigation Strategies	1

Source: FDA https://www.fda.gov/media/145858/download

“Remote Interactive Evaluations”

- FDA Guidance, *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 14, 2021) (https://www.fda.gov/media/147582/download)
  - Human and animal drugs and biologics
  - FDA will determine sites based on risk—no requests
  - If FDA decides that a remote evaluation is appropriate, the agency and the company will have a videoconference to discuss logistics, responsibilities and expectations
    - Topics will include the identity of the FDA team, scope of the evaluation, information technology requirements, methods for sharing documents, and timing
  - Documents must be provided in a reasonable timeframe, and the agency may have spontaneous discussions with employees during business hours
  - FDA will use its own conferencing platforms
  - No 483s but will have a closeout meeting and provide written observations

“Remote Interactive Evaluations” (cont’d)

- Remote interactive evaluations are not technically “inspections” under the Federal Food, Drug, and Cosmetic Act
  - However, FDA will use the information collected to decide whether to approve an application; to decide whether a physical inspection is needed; and to support an import alert, warning letter, recall request , or other compliance or enforcement action
  - The agency also states that it will use information from evaluations to meet its user-fee timeframes and that it “generally intends to use existing timelines established for reporting on and evaluating the outcome of an inspection for the remote interactive evaluation”
  - However, “[d]eclining FDA's request to perform a remote interactive evaluation could impede [the agency’s] ability to make a timely regulatory decision (e.g., regarding adequacy of a clinical trial used in support of a pending application or adequacy of a drug manufacturing operation described in the application)”
    - May accelerate an in-person inspection

Transitioning Back to Standard Operations

- Base case assumes FY 2021 focus on mission-critical and prioritized domestic inspections through July 2021, and then resuming standard operations

Commodity	FDA Domestic Remaining through FY21	Base-Case Scenario Estimated Domestic Achievable FY21
Human and Animal Food	12,285	1,272 (10%)
Human and Animal Medical Products	3,229	851 (26%)
Grand Total	15,514	2,123 (14%)

COVID and Real-World Evidence

- FDA policy development on RWE has been a major focus for several years—use in approvals, promotion, etc.
  - COVID intensified this focus due to problems in trials, changing standard of care during pandemic, etc.
- Increasing use of RWE to understand standard of care and patient experience—driven by expansion of electronic health records and artificial intelligence
- Potentially broader use of RWE as an external or "synthetic" control arm—particularly for rare diseases, oncology
- Upcoming user fee reauthorization likely to further accelerate these developments

Clinical Trial Agreements and Related Documents

Clinical Trial Agreement—COVID-19 Negotiation Impact

- Study initiation halted
- Delays
- Longer than usual review (at all levels—IRB, contracts, study staff/coordinator/PI, budget/finance)
- On-going studies—protocol amendments and ICF amendments
- Ex-US
  - Europe (originals, ICFs)
  - Canada (closed borders)
  - Australia (shut down all studies)

Clinical Trial Agreement—COVID-19 Terms/Provisions

- Unique provisions raised during COVID-19
  - Specific COVID-19/pandemic provision
    - Permitted delays in study activities with notification
    - Add language for continuing updates (commencing or continuing study)
  - Force majeure provision (addition of COVID-19/pandemic provision)
    - Add language regarding notification and mitigation/reducing impact
    - Extension of time for performance that is equitable in light of cause of delay
    - Limit remedy for right of termination
  - Remote monitoring
    - Acceptance of third-party terms
    - Acceptance of institutional policies/procedures
      - Detailed data security/breach notification provisions (signed by third parties)
    - Acceptance of additional confidentiality/remote access agreements

Clinical Trial Agreement—COVID-19 Terms/Provisions (cont'd)

- Unique provisions raised during COVID-19 (cont'd)
  - Alternative audit language
    - Remote audit/investigation process in lieu of direct participation
  - Adding alternative facilities/clinics
    - Addressing inter-institutional arrangements
    - Addressing study staff responsibility/liability
    - Addressing access
    - Separate Facility Use Agreement
  - Addition of Network Security & Privacy (Cyber Liability) Insurance coverage
  - Limitation of Liability—removal of liability for failure or delay

Clinical Trial Agreement—COVID-19 Process Issues

- Remote monitoring
  - CROs/auditors
    - Third-party access/platform
    - GDPR
  - ICFs

Clinical Trial Agreements and COVID-19 Impact

- Short term
  - Impact on protocol mandated visits (testing & procedures)
    - Home visits by third-party vendor to collect vitals
    - Third-party vendor to distribute drug
  - Impact on supply chain for Study Drug to sites
    - Impact on carriers/shippers
  - Remote monitoring
- Long term
  - Remote monitoring
  - Increased use of technology tools

eCOAs/ePRO

- A Clinical Outcome Assessment (COA) is a measure that describes or reflects how a patient feels, functions or survives
- A PRO is a type of COA
  - Patient Reported Outcome (PRO): A measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else
    - ePRO refers to information provided directly from the patient about symptoms, side effects, drug timing, etc. captured on an electronic device

BYOD—Bring Your Own Device

- Patients to use their own smartphone or Internet-enabled device to complete study assessments
  - Sponsor benefits
    - Reduction in cost and logistical burden
    - Increase in compliance
  - Patient benefits
    - Ability to use the device that they are familiar with
    - Reduces the burden of having to carry multiple devices

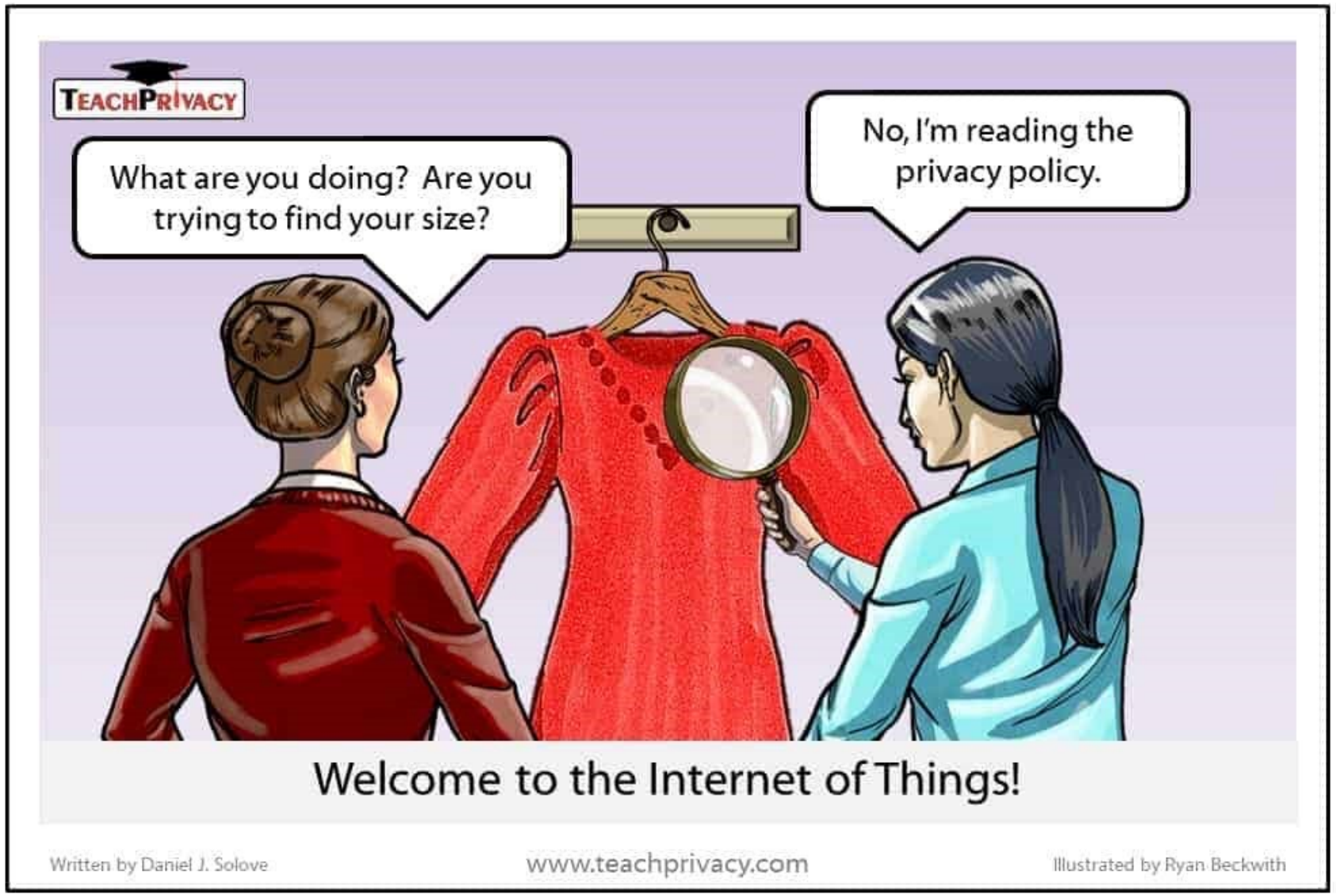
Managing Data-Related Risks in Digital Health Contracts

- Address data security and breach risks and responsibilities
  - Set forth clear processes and remedies in advance
    - Including communications with regulators and other breach-related notifications
  - Audits
  - Allocate any associated costs
  - Consider corporate compliance policies
- Indemnification
  - Generally: Covers breaches of the agreement, including breaches of applicable law and data-related reps, warranties and covenants
- Insurance
  - Cyber-insurance may be particularly important
    - Particularly important when the counterparty is a start-up
- Limitations of liability
  - Indemnification, breaches of confidentiality and breaches of data protection obligations are typically uncapped

Fact-Specific Mitigation Considerations

- Is the technology provider obligated to mitigate or does it have a right to mitigate?
- Indemnitee may want to have the right to elect a remedy
- Indemnitee may want to require that substitutes or modifications provide equivalent performance, functionality and efficiency
- If termination or refund is an option, indemnitee may want to ensure that it is not available unless none of the other options are possible/practicable
- If termination or refund is an option, indemnitor may want to ensure that refund is reduced in relation to the amount of time the indemnitee has been able to use the IP/licensed technology

Patient Contract Issues



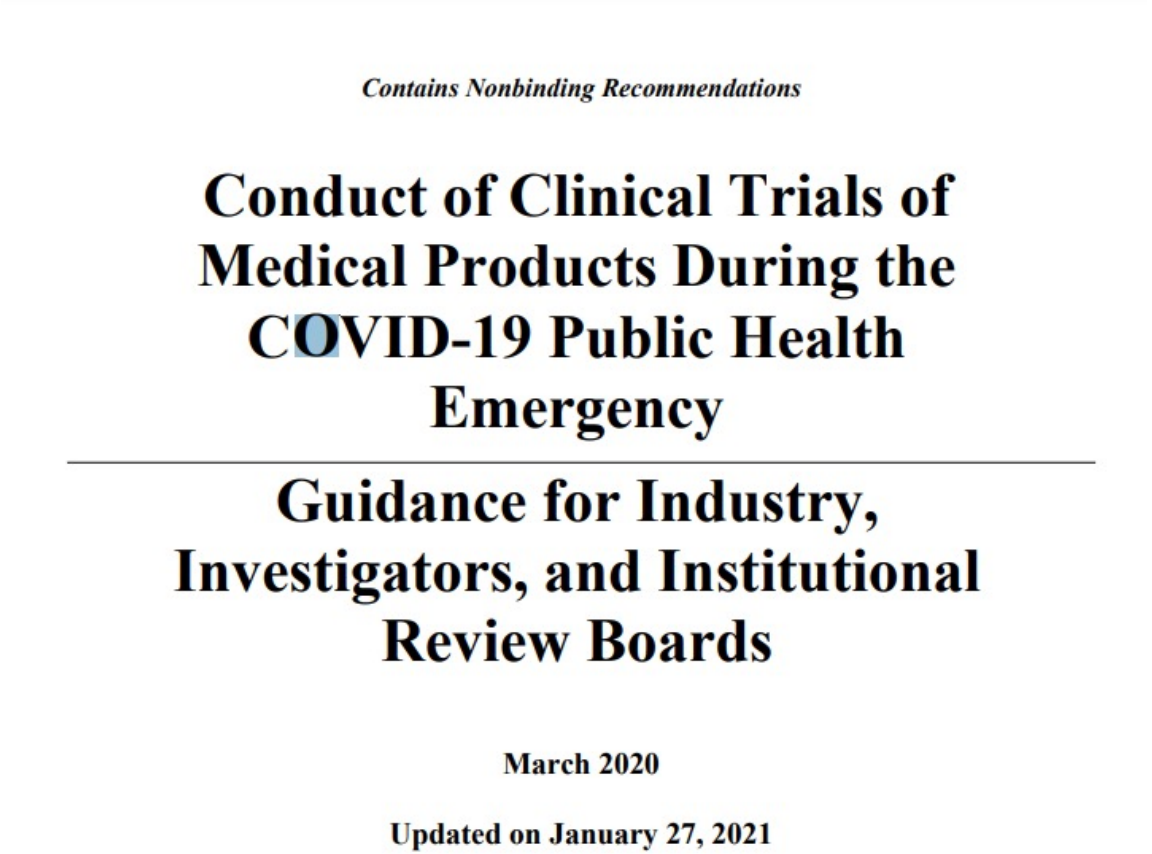
Privacy and Cyber Considerations

More Data = More Privacy

- More Data in Clinical Trials = More Privacy and Cyber Considerations
- In remote clinical trials—sponsors, CROs, others may have access to more identifiable and electronic data
- Use of patient-focused apps and wearables adds even more data and systems outside of the traditional systems used for clinical trials
- Depending on who is hosting the app/facilitating remote monitoring/etc., it may be difficult to pseudonymize (key-code) the data
  - Need to protect it AND
  - Need to segregate it from other identifiable data
- Consider data minimization

Remote Clinical Trials—Privacy Considerations

- FDA guidance from March 2020, updated as of December 4, 2020, on conducting remote clinical trials contain key privacy considerations
  - Ensuring that remote data acquisition, transmission and storage are secure
  - Protecting the privacy of participants, including procedures for assessing and confirming the safety of trial participants' privacy
  - Using automated audit trails when using electronic platforms to perform remote assessments that transmit data directly into trial records
  - Authenticating and verifying identity and otherwise ensuring privacy and security in videoconferencing



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Use of Deidentified and Anonymized Data in Clinical Trials

- Understand the context in which the data/samples were collected
- Transparency is key—were individuals told about the deidentification and anonymization of data?
  - Is consent necessary?
- Ensure appropriate procedures are in place to prevent reidentification
- Understand differences in global privacy laws and how that impacts removal of identifiers from data
  - US—deidentification under HIPAA—data can be key-coded
    - That is pseudonymized data under many other privacy laws
  - Anonymized data cannot be key-coded or otherwise able to be reidentified

The Cyber Threat During the Pandemic

- "Federal prosecutors . . . are seeing a rise in cyberattacks on the health-care industry."
  – *Wall Street Journal*, June 17, 2020
- **"We've seen cyberattacks on health care, pharmaceutical and research organizations in order to steal valuable research on coronavirus vaccines and treatments."**
  – *Brian Benczkowski, Chief of the Criminal Division, US Department of Justice*
- April 8, 2020: UK's National Cyber Security Centre (NCSC) and US DHS Cybersecurity and Infrastructure Security Agency (CISA) exposed malicious cyber actors using COVID-19-branded scams for hacking purposes
- July 16, 2020: NCSC exposes Russian cyber actors targeting organizations involved in vaccine development and others involved in COVID-19 response
- December 9, 2020: European Medicines Agency, while working on vaccine approvals, released news of a cyber attack related to vaccine documents

How to Control the Cyber Threat?

- Policies and Governance
- Risk Assessment and Management
- Access Controls
- Encryption
- Vulnerability Management
- HR Procedures
- Detection
- Audit
- Third-Party Management
- Physical Security
- Business Continuity and Disaster Recovery
- Incident Response and After-Action

Audit, Assess, Oversee

- Check in on systems containing troves of identifiable patient data
- Make sure your third parties are adequately protecting data—not only through contract but through information security questionnaires, assessments and auditing
- Think about and consider how data will be stored after the end of the trial—how to delete, what to keep, etc.
- Critically—limit access and onward uses of patient data

Questions & Answers

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- Alice Um Kope is Assistant General Counsel at Atara Biotherapeutics, an immunotherapy company, for the past five years supporting a number of legal activities/departments, particularly involving the company's various clinical studies—including handling clinical trial agreements, informed consent reviews, CRO/vendor agreements, privacy and data security issues, and clinical product issues.
- She is also the current Vice President, Operations for the San Francisco Bay Area Chapter of the Association of Corporate Counsel.
- Prior to being at Atara, she has been with a number of small and large biotech/pharma/device companies providing advice on and assistance in negotiating and documenting commercial relationships, compliance and business matters over a broad range of business relationships, including vendors, collaborators, clinicians, and business partners.

Vinita Kailasanath

Partner, Technology Transactions & Life Sciences Transactions
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- Drafts and negotiates contracts for the commercialization and protection of intellectual property and technology, as well as advises clients on issues at the intersection of intellectual property and FDA regulation.
- Routinely assists leading life sciences companies and technology solutions providers with collaboration agreements, license agreements, development agreements, M&A, joint ventures, supply agreements, clinical trial agreements, software as service arrangements, terms of use, privacy policies, sweepstakes and contest rules, and other technology and intellectual property-driven transactions.
- Has helped bring many novel products to market, including medical devices, healthcare apps, mobile technologies, software offerings, and cloud-based platforms.
- Identified as a Northern California “Rising Star” (2018-2020) by *Super Lawyers* and "Next Generation Partner“—Healthcare: Life Sciences (2020) by *The Legal 500 US*.

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- Co-chair of the Life Sciences and Healthcare Regulatory Practice.
- Represents pharmaceutical, biotechnology, medical device and diagnostic companies, including start-up companies, trade associations and large manufacturers.
- Negotiates challenges relating to the full product life cycle to include development, approval and marketing of FDA-regulated products.
- Regularly handles product and compliance-related government and internal investigations, the development of global corporate compliance programs, and due diligence in financings, mergers and acquisitions.
- Counsels on biomedical public policy matters including congressional investigations and on FDA-related legislation.
- Advises on matters relating to foods, dietary supplements and cosmetics.

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- Aids clients in developing digital health, artificial intelligence and other technology solutions to augment consumer, customer and patient engagement and in designing new data-driven technology, products and services in a forward-looking, flexible and ethical manner.
- Counsels on compliance with the ever-growing number of data protection requirements and on how to create global data strategies designed to align with these requirements in an efficient, proactive and operationalized way.
- Negotiates privacy and data security provisions with customers and third parties, including Business Associate Agreements, and creates customer-facing materials to explain data protection measures.
- Engages in privacy and data security due diligence for mergers and acquisitions.
- Assists in program and policy creation, conducts privacy and data security risk assessments, and advises on data risk management.
- Defends clients in privacy and data security-focused investigations by state attorneys general, the Department of Health and Human Services Office for Civil Rights, Federal Trade Commission, and other data protection regulators.

Questions?

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