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Happy Trials to You!

IN THIS ISSUE

The Slippery Slope into Research Misconduct: Research Records

By Shelley Bizila and John R. Baumann

When we think of research misconduct, what generally comes to mind are the biggest cases: Wakefield (MMR and autism), Hwang (production of human embryonic stem cells) and Croce (cancer). These cases resulted in newspaper headlines, a multitude of retractions and likely other sanctions that were not reported. But even seemingly innocuous practices may result in research misconduct allegations that create, at best, an inconvenient disruption and, at worst, an actual finding of research misconduct that can lead to career-ending consequences. In the hurried, fast-paced world of clinical and translational research, it is easy to make a mistake or take a "harmless" shortcut. When time is short and the days are overwhelming, it can be tempting to try to cover up those errors or "correct" them without documentation or telling anyone. What may seem innocuous can snowball into something disastrous. Alternatively, errors can avoid becoming research misconduct with timely reporting, correction and mitigation.

What Is Research Misconduct?

The Public Health Service defines research misconduct as follows:

see **The Slippery Slope** on page 5

How to Be Heard Loud and Clear in a Complex Organization

By Kristy Averett

Anyone who has worked in clinical research for a few years is aware that the complexity of clinical trials has increased over time. There now seems to be a different online platform or a separate office for nearly every aspect of a trial, especially at large organizations like academic medical centers (AMCs) and pharmaceutical companies. Increasing complexity and fragmentation of responsibilities means that communication requirements have increased exponentially. Depending on your role, you may have to communicate regularly or from time to time with hundreds of people.

Not only must each communication be clear, but it must also go to the correct people in the correct form at the correct time. Just keeping track of who needs which communications, how and when they prefer to communicate, and the technology they prefer to use has become a major undertaking. To compound this problem, the rapid rate of technology adoption and people moving in and out of positions means that everything is in flux. Misunderstandings can easily arise from hurried or delayed

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ON SITE

Clinical Research Forum Names Top 10 Research Efforts of 2021

By James Miessler

The Clinical Research Forum, a nonprofit organization based in Washington, D.C., has unveiled its picks to receive its annual Top 10 Clinical Research Achievement Award, a recognition it gives to researchers who are exceptionally innovative and impactful on a number of diseases.

The following clinical research activities received the 2022 Top 10 Clinical Research Achievement Award:

- Duke University's "ADAPTABLE" (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) trial
- Regents of the University of California — Davis' "Association of Dose Tapering with Overdose or Mental Health Crisis Among Patients Prescribed Long-Term Opioids" study
- University of California — Los Angeles' "Behavioral Nudges Increase COVID-19 Vaccinations" trial
- Cleveland Clinic's "Neurorobotic Fusion of Prosthetic Touch, Kinesthesia and Movement in Bionic Upper Limbs Promotes Intrinsic Brain Behaviors" study
- The National Cancer Institute Center for Cancer Research's "Development of Pomalidomide in the Treatment of Chronic Graft vs. Host Disease" trial
- Stanford University's "Evaluating Eligibility Criteria of Oncology Trials Using Real-World Data and AI" study
- Tufts University's "New 'Race-Free' Equation to Estimate Kidney Function" and the University of California — San Francisco's "Race, Genetic Ancestry and Estimating Kidney Function in Chronic Kidney Disease" studies (which shared an award)
- Northwestern University Feinberg School of Medicine's "Once-Weekly Semaglutide in Adults with Overweight or Obesity" trial
- Rockefeller University's "The Important Role of Autoantibodies Neutralizing Type I IFNs in COVID-19" study
- University of Pittsburgh's "Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media" study.

The top three winners, to be chosen from the top 10, will be announced on April 19 and will receive cash awards; one will receive a cash prize of $7,500 while the other two will receive $5,000 each.

A total of 70 nominated trials and studies published in peer-reviewed journals in 2021 were judged by the Clinical Research Forum's board based on the trials' impacts, outcomes and/or designs. The forum shared with *CenterWatch Weekly* its reasoning for selecting the winners.

Stanford's "Evaluating Eligibility Criteria of Oncology Trials Using Real-World Data and AI" study was selected based on its clinical research impact. The study's methodology could be widely adopted in clinical research to make trials more inclusive, safe and efficient and is, in fact, already being utilized by Roche and Genentech in their trial designs. The trial featured Trial Pathfinder, an open-source software tool that evaluates the impact of different eligibility criteria on patients and can be used in other trials.

Duke's ADAPTABLE trial featured a pragmatic trial design that was able to answer a longstanding question about aspirin-dosing guidelines for heart disease patients. It was the first clinical trial to use the National Patient-Centered Clinical Research Network (PCORnet), a data, research and patient insight network, to do comparative-effectiveness research.

One study was awarded based on its impact for patients tapering off opioids, as its findings showed that patients on long-term opioid therapy are more vulnerable as they taper off. The findings from UC Davis' "Association of Dose Tapering with Overdose or Mental Health Crisis Among Patients Prescribed Long-Term Opioids" may lead to a more careful, supportive approach when adjusting opioid doses and will likely end the practice of rapid and involuntary tapering.

The UCLA "Behavioral Nudges Increase COVID-19 Vaccinations" trial was deemed significant because it revealed things that could impact whether people get vaccinated. It found that behavioral science can accelerate uptake of COVID-19 vaccinations without much marginal cost and suggested that behavioral nudges, such as positive reinforcement, may be a viable and effective promotional strategy for vaccination.

Researchers made significant headway in the treatment of advanced chronic graft vs. host disease (cGVHD), a rare disease that affects patients after a stem cell or bone marrow transplant. The National Cancer Institute Center for Cancer Research's "Development of Pomalidomide in the Treatment of Chronic Graft vs. Host Disease" trial showed that low doses of pomalidomide, a treatment for relapsed/refractory multiple myeloma, are safe and effective for treating cGVHD and also identified biologic mechanisms that

see **Top 10 Research Efforts of 2021** on page 7

BOOK REVIEW

The Practical Guide to Clinical Research and Publication

Uzung Yoon, 2021, 208 pages, Academic Press, $84.95

Review by Norman M. Goldfarb

The Practical Guide to Clinical Research and Publication provides basic information about conducting and publishing clinical research studies in a compact form for academic researchers.

The following extract from the section on research questions illustrates the compact presentation:

Research question:

- To formulate a research question, extensive knowledge on that particular topic is required.
- An appropriate research question can only be worked out if there is enough knowledge of the topic and the current research trend.
- A literature and database search to that particular topic is strongly encouraged.
- Expert consultation or mentorship may be required.

A research question should be

- **Clear:** Specific and detailed enough so that the reader can easily understand the purpose.
- **Focused:** Narrow enough that it can be answered thoroughly.
- **Concise:** Brief but comprehensive.
- **Novel:** A new concept or approach.
- **Original:** The principal investigator should synthesize an original concept with his unique knowledge that is not available in the same form from previous studies.
- **Knowledge contribution:** What is already known about that topic? What is the new knowledge to be gained with this research question?

The research question is the single most important part in a study design!

Each clinical trial must have a primary question. The primary question, as well as secondary or subsidiary questions, should be carefully selected, clearly defined and stated in advance.

PICO

Formulating a research question with the PICO criteria:

- The PICO criteria (Population, Intervention, Control and Outcome) developed by McMaster University is a helpful tool for creating a structured research question.

TABLE 5.1 Formulating a good and poor research question

	Good Research Question	Poor Research Question
Population	Coronary Artery Disease with >70% stenosis; patients between 60 and 70 years old	Heart-sick people
Intervention	1 hour treadmill every day at 5 km/h	Sports
Control	No treadmill	No sports
Outcome	Heart attack confirmed by EKG and troponin	Heart attack

- Present the research question systematically and clearly.
- The Cochrane Collaboration recommends use of the PICO criteria in the process of formulating a research question (Table 5.1).
- A good research question is precise and well-defined and can be obtained using pre-existing research methods.
- The excerpt does not illustrate the book's heavy use of diagrams to clarify the material.

The book includes 15 chapters:

- Introduction
- Evidence-based medicine
- Epidemiology
- Biostatistics
- Planning a research study
- Study design
- Hierarchy of evidence
- Funding
- Data collection
- Scaling and coding
- Statistical tests
- Random and systematic errors
- Writing a manuscript and publication
- Critical literature review
- Checklist for quality assessment

Reviewer

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GOOD CLINICAL PRACTICE Q&A

Focus on SAEs

What do you do when you find an adverse event in a patient chart, for example, when auditing several years after the patient was on study and that event constituted an SAE that should have been reported even if it was unrelated to the drug (e.g., hospitalization) but there is no documentation in the chart that it was reported?

Since it is often several years after the close of a clinical study before a sponsor submits the results in support of a marketing application to FDA, the sponsor should be contacted to determine if the potential SAE had, in fact, been reported. If not, it should be reported, complete with as much information as known at the time. Additionally, there have been times when seemingly unrelated SAEs have been revealed to be related to use of the drug when information across multiple sites is compiled, with larger numbers making rare events apparent.

Source

"Good Clinical Practice: A Question & Answer Reference Guide," Barnett International. The Guide is available at http://www.barnettinternational.com in electronic and paper form.

GCP REGULATORY ROUNDUP

Recent Good Clinical Practice and related news from FDA, EMA and other sources

FDA Resumes Domestic Inspections

The FDA resumed normal domestic inspections of device facilities last month, citing the declining rates of COVID-19 cases across the country. The FDA had announced on Dec. 29 that it was temporarily suspending many of its domestic and foreign inspections due to the fast-spreading SARS-CoV-2 Omicron variant. The agency said it will continue to use a variety of tools to conduct both domestic and foreign mission-critical inspections, including remote assessments. Previously planned foreign surveillance inspections that have received country clearance and are within the Center for Disease Control and Prevention's COVID-19 travel recommendation also will proceed, the agency said.

UK Calls for Comments on Proposals to Improve Clinical Trial Laws

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) is seeking public comment on proposals to update the UK's clinical trial legislation. No longer part of the European Union, the UK wants to update its clinical trial legislation to improve trials across the board. Specifically, the MHRA aims to streamline its trial approval process, encourage innovation in clinical research, improve the transparency of trials and spur greater patient and public involvement in trials. The agency is hoping for useful feedback to give it direction in its trial reforms. The comment period is open until March 14. Read the full proposals here: https://bit.ly/3gwht0V.

CDER Issues Guidance Agenda for 2022 Featuring Clinical Trials

The FDA's Center for Drug Evaluation and Research's (CDER) guidance agenda for 2022 includes eight draft guidances for clinical trials the center hopes to release before the end of the year.

Topics of trial-related draft guidances on the list include: Decentralized clinical trials; Using clinical practice data in randomized controlled trials for drugs and biologics; Considerations for designing and conducting externally controlled trials for drugs and biologics; Determining good cause for noncompliance on periodic status reports required in certain cases for postmarketing studies and clinical trials; Inborn errors of metabolism that use dietary management: considerations for optimizing and standardizing diet in clinical trials for drug product development; Measuring growth and evaluating pubertal development in pediatric clinical trials; Meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation and confirmatory evidence; and Use of data monitoring committees in controlled clinical trials.

Five of the eight trial-related draft guidances on this year's list are carryovers from 2021. The list does not include any final trial-related guidances CDER plans to issue in 2022. Read the 2022 FDA guidance agenda here: https://bit.ly/3LlPOxJ.

The Slippery Slope

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Research misconduct means fabrication, falsification or plagiarism in proposing, performing or reviewing research or in reporting research results.

- Fabrication is making up data or results and recording or reporting them.
- Falsification is manipulating research materials, equipment or processes or changing or omitting data or results such that the research is not accurately represented in the research record.
- Plagiarism is the appropriation of another person's ideas, processes, results or words without giving appropriate credit.

Research misconduct does not include honest error or differences of opinion.

The research misconduct regulations define a "research record" very broadly. Institutions may use more granular definitions, such as the following:

A research record is any data, document, computer file, digital medium or any other written or nonwritten account or object that reasonably may be expected to provide evidence or information regarding the proposed, conducted or reported research that constitutes the subject of an allegation of research misconduct. It includes, but is not limited to, grant or contract applications, whether funded or unfunded; grant or contract progress and other reports; laboratory notebooks; notes; printed or electronic correspondence; memoranda of telephone calls; videos; photographs; X-ray film; slides; biological materials; computer files and printouts; manuscripts and publications; equipment use logs; laboratory procurement records; animal facility records; human and animal subject protocols; consent forms; medical charts; and patient research files.

Allegations of fabrication, falsification or plagiarism can extend beyond the realm of research findings and publications. Rather, because of the importance of protecting the integrity of the research process writ large, any failure to ensure that the records match the actual practice of research can result in an allegation of research misconduct. Research misconduct includes, but is not limited to, the following acts, even if it may not actually affect the final research findings or results:

- Altering eligibility dates, test results etc.
- Creating documentation for visits/tests/interactions that did not exist
- Eliminating outlier data without so stating
- Falsely reporting the number of study subjects
- Back-dating consent forms/authorization forms
- Falsely reporting the credentials of study personnel.

Examples

The following are a few examples of actual research misconduct cases that have come to the attention of the authors:

Example 1

A Research Coordinator (RC) is in charge of a very complex clinical trial involving hundreds of subjects. Her duties include dispensing medications, enrolling subjects, scheduling quarterly visits, tracking medical records, making payments to subjects, etc. She has been around forever — before background and degree/license checking — so no one questions her credentials, experience or performance. The RC begins falling behind in her heavy workload. The Principal Investigator (PI) does not respond to her requests for help because she is a superstar scientist who does not have the time or open mind for complaints. The PI often travels to give lectures, etc., so she is not onsite on a regular basis. She knows the RC has always managed just fine through challenging periods in the past.

The RC then has a medical event involving neurological issues. She eventually returns to work at half-capacity, but her work has really piled up. The PI does not want to use her funds to hire another RC. In her haste to catch up, the RC begins to make mistakes and tries to cover them up by indicating visits, etc. that did not occur. Subject medications come up missing. The study sponsor notices and reports some problems to the PI, who promises more oversight but does not deliver.

The PI has signed off on the delegation log attesting to the RC's qualifications. The PI subsequently becomes aware of the RC's false credentials but does not act.

The institution receives a report about the situation. Its investigation determines that the RC falsified documentation. While the PI did not falsify anything, her lack of oversight contributed to research misconduct.

Observations: In this example, the definition of "research record" is critical. While no publications had yet resulted from the research activity, the institution's definition of "research record" led to a finding of falsification of credentials and subject records. The institution found both the PI and RC at fault.

Example 2

A graduate student research assistant (RA) funded on an NIH study was expected to conduct an intervention on and monitor a rack of rats over the weekend. These tasks slipped her mind until Monday morning, when she quickly wrote her "observations" in the lab book. A few days later, the PI saw notations in the lab book that seemed a bit irregular. She contacted the Research Integrity Officer (RIO) with her concerns.

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The Slippery Slope

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The RIO then contacted the RA, who confirmed that she had performed the tasks on Saturday and Sunday as required. When confronted with the fact that there was no record on the card access logs of her entering the facility, she claimed she had "piggy-backed" on someone else's entry. When asked to identify who that was, she finally admitted her failure to work in the lab over the weekend and falsely recording that she had done so.

Observations: While not following approved protocol procedures is obviously a protocol violation, the activity also became research misconduct when the RA recorded in laboratory records that she had completed procedures which she in fact had not. The coverup is what made it research misconduct, not the failure to conduct the work over the weekend.

Example 3

The PI of a federally funded study of noninjecting heroin users was accused by another researcher, after reading his publication, of having dropped data points and in other ways conducted the data analysis in a manner designed to get the results he wanted. This person then submitted an allegation of research misconduct to the RIO. During the assessment of the allegation, although it was determined that the statistical analysis was indeed, at minimum, problematic, it was dropped as a research misconduct case because the publication included a footnote with an extensive description of what he had done with the data.

Observation: While the strategy for organizing and analyzing the data may be controversial or even scientifically "wrong," it was not research misconduct, since the research record identified everything the PI did with the data.

Example 4

A federally funded study was being conducted on the experiences of drug addicts who overdose and end up in the hospital's emergency room. The researchers trained assistants (former addicts) to approach the patients, obtain informed consent and record their answers to survey questions during a meeting. Participants who agreed were given gift cards and vouchers for transportation from the hospital. One of the assistants observed another assistant entering data after, not while, meeting with patients. In addition, time spent with participants appeared to be too short to obtain informed consent and properly complete the survey. An investigation determined that the assistant in question was completing the informed consent and survey forms without the patients' involvement.

Observation: While this matter is clearly a human subjects violation, it also became research misconduct because research records (informed consent and survey forms) were falsified.

Prevention and Mitigation Strategies

Institutions may develop and implement a wide variety of approaches to reduce and even prevent practices that may result in research misconduct. At minimum, institutions should roll out a robust outreach program of education throughout their research communities, as well as other resources and tools. The following approaches have been found to be very useful:

- Conduct an educational program, including webinars and workshops focused on both big picture and very specific areas of research misconduct, using real-world examples, such as those above, to diverse audiences, such as:
  - — Academic unit and departmental faculty meetings
  - — Research coordinators
  - — Other compliance committees
  - — Create a standing committee of senior, experienced researchers with diverse and relevant expertise who can contribute to inquiries and investigations, and who can also serve as ambassadors within their academic units and departments
  - — Provide guidelines, requirements and tools for data reporting/documentation, management and retention, as well as institutional resources for quality assurance checks
  - — Provide continuing medical education credits for individuals who attend research integrity training sessions, contribute to investigations and make quality assurance checks.

Conclusion

As the above examples reveal, research is a complicated and very human process. Everything must be properly carried out. It must also be properly documented — but only if actually carried out. At times, researchers may fail to carry out processes as required. But, as illustrated in the examples above, such failures can grow into something qualitatively different and more serious when there is an effort to cover up the initial failure by fabricating or falsifying the research record. As we see so often in politics, business and other arenas, the coverup is often more serious than the original offense.

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Complex Organization

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electronic communications, especially email, between people from different cultures and from different generations.

In addition to the study team itself, AMCs have various therapeutic departments and different offices for regulatory compliance, ethical review, contracts, budgets, billing, pharmacy, etc. Study sponsors have their own organizational complexities, often including numerous solution providers that can vary from study to study. And we cannot forget about study participants.

To communicate effectively, your first task is to create and maintain a list of the people with whom you communicate. You can maintain this list in a spreadsheet, a database or on paper, depending on the size of your list and your own preferences. Your list should include, at minimum, people with whom you communicate regularly and people whom you may need to contact on short notice about important matters (e.g., technology platform technical support). In addition to their roles and contact information, you can add notes about their communication preferences to your list. For example, do they prefer face-to-face conversations, emails, telephone calls (office or home), online meetings (Zoom, Teams, etc.) or online forms? What time zone are they in? Do they prefer to schedule communications in advance? Do they have an online directory you can check for current contact information?

You probably will not have time to periodically verify all the information in your list, but you can certainly update it when you notice a change. If multiple people in your organization are communicating with the same people, you can maintain a shared list.

Many of the people you communicate with probably share your communication challenges. Help them out by including your contact information in your email signature. You may want to send some people an email with more complete contact information and your own communication preferences.

The current remote-work environment justifies the following reminders for effective communications:

- Communicate in a manner that builds relationships, even in remote communications.
- Maintain a demeanor that is friendly, respectful, professional and as positive as possible, no matter how many promises they have broken, how badly they are behaving or how pressing your emergency.
- Remember that you are not only representing yourself, but also your team and organization.
- Choose the best medium of communication — email vs. phone call vs. meeting — based on the nature of the exchange and people's preferences. Do not be afraid to suggest changing the medium.
- Communicate in a timely manner; do not keep people waiting longer than necessary for a reply.
- Be clear in your communications. Especially when you are asking someone to do something, provide context and specifics to avoid errors, delays and further exchanges for clarification.
- Use out-of-office messages appropriately when people cannot expect a timely response.
- Spare a minute to engage about something outside the task at hand.
- If you are stressed out, tell people, so they can make allowances.

As a final note, remember that electronic messages can live forever and end up in the hands of people not intended to see or hear them. Messages that contain confidential information or display unprofessional behavior can damage you, your organization and the mission of clinical research.

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could lead to new targeted therapies and drug combos for the disease in the future.

Tufts' and the University of California, San Francisco's studies, which shared an award, were selected because of their findings in assessing the impact of race on kidney function assessments. The University of California — San Francisco's study demonstrated that the race coefficient should not be completely taken out of estimating glomerular filtration rate (GFR), a measure of how well the kidneys filter blood, when using tests that rely on creatinine as their filtration marker. It also showed that race doesn't need to be factored in when using cystatin C, another test, which should move healthcare practice toward greater adoption of it. The Tufts study demonstrated that the Chronic Kidney Disease-Epidemiology (CKD-EPI) is a reliable equation for computing and reporting estimated GFR and also doesn't require input of race. This method is already being adopted for the large share of minorities who suffer from chronic kidney disease.

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Top 10 Research Efforts of 2021

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Revealing the significant weight loss provided by once-weekly semaglutide, a drug that is infrequently considered a treatment option for obese patients due to multiple barriers, was lauded for work done by researchers at Northwestern University Feinberg School of Medicine's "Once-Weekly Semaglutide in Adults with Overweight or Obesity." They discovered that a weekly 2.4-mg dose of semaglutide for 68 weeks led to an astounding 15 percent average weight loss, with one-third of participants shedding weight comparable to that seen from bariatric surgery.

Rockefeller University's "The Important Role of Autoantibodies Neutralizing Type I IFNs in COVID-19" was awarded based on its contributions to understanding COVID-19. The researchers identified a group of individuals with specific genetic deficiencies that may be predisposed to more severe COVID infection. These patients can be identified using exome sequencing and plasma analyses.

A study that evaluated a bionic arm in amputees delivered a method to measure the sensory and motor features of the arm, essentially assessing how much patients felt like it was a real limb. The Cleveland Clinic's study was awarded because it will contribute improvements to the feasibility and usability of bionic limbs.

And lastly, the forum awarded the University of Pittsburgh's "Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media" study because the findings are likely to lead to a major shift in how otitis media (ear infection) is managed in children. Specifically, the study found that tympanostomy tubes did not offer advantages in reducing the rate of ear infections and that antibiotic treatment was the best option for most children who suffer from recurrent ear infection.

This story first appeared in CenterWatch Weekly.

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BOOK REVIEW

Outbreaks: A Practical Legal and Risk Management Primer for the Healthcare Sector

Leanne E. Tran, 2022, 749 pages, LexisNexis, $160

Review by Norman M. Goldfarb

Outbreaks: A Practical Legal and Risk Management Primer for the Healthcare Sector expertly covers a vast topic essential to attorneys and risk managers in the Canadian healthcare sector. The book also discusses the recent history and implications of COVID-19 in what must have been a herculean task for the author.

The following extract illustrates the book's discussion of clinical research regulation in Canada:

Regulatory Process for Medical Devices

Medical devices are divided into four classes (Class I-IV) under the Classification Rules set out in Schedule 1 of the Medical Devices Regulations. Class I represents the lowest risk and Class IV represents the highest risk. If a medical device can be classified into more than one class, the class representing the higher risk applies. The risk classification scheme divides devices into in vitro diagnostic devices (IVDD) and nonIVDD, the latter being further grouped into four sets: invasive devices, noninvasive devices, active devices and special rules.

The Canadian classification rules use the following indicators of risk: degree of invasiveness, duration of contact, body system affected and local vs. systemic effects. Duration of use of the device is also taken into consideration. Health Canada provides guidance documents to help manufacturers establish the correct classification for their device. However, Health Canada has the final decision if there is any dispute.

The following extract illustrates the book's discussion of COVID-19 events and considerations:

Changes to Pharmaceutical and Medical Device Regulations: COVID 19 Drug and Medical Device Importation, Sale and Clinical Research

Under the Food and Drugs Act, the Minister of Health has the power to issue interim orders to allow certain drugs and medical devices that may not otherwise fully meet regulatory requirements to be sold and imported into Canada. The interim orders issued during the early months of the pandemic offered a fast mechanism to prioritize and expedite the regulatory review process to access COVID-19 health products.

On Feb. 4, 2020, a publication found that remdesivir and chloroquine were highly effective in the control of 2019-nCoV infection in vitro. A flurry of follow-up research and clinical trials occurred. On March 31, 2020, a small randomized clinical trial testing hydroxychloroquine in Wuhan, China, published data that reported improvements in time to clinical recovery. These early studies were often very small

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and time-limited, but satisfactory enough to explore these drugs in larger, randomized clinical trials. Despite only having basic preliminary data, former U.S. President Trump began to publicly support the use of hydroxychloroquine as early as March and pushed for the U.S. Food and Drug Administration (U.S. FDA) to approve its use. Former President Trump continued to support its use in the population as a preventative measure, stating he was taking it prophylactically, even as studies emerged about severe adverse events and cautioning its use outside a hospital setting. On June 15, 2020, the U.S. FDA finally revoked its March 28, 2020, Emergency Use Authorization (EUA) for the use of hydroxychloroquine in certain hospitalized patients after having issued safety warnings in the preceding months. In early July, the World Health Organization (WHO) discontinued the hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 based on the Solidarity Trial's International Steering Committee's recommendation. This came after the WHO temporarily suspended hydroxychloroquine clinical trials as a precaution on May 25, 2020, based on a (later retracted) study published in *The Lancet*, and then resumed testing a little over a week later after reviewing the evidence.

From a clinical research perspective, some of the most challenging aspects have been designing trials in real-time, conducting human trials during isolation orders, enforcing physical distancing, balancing the need to generate conclusive evidence against the immediate needs of patients to access effective therapeutics, knowing when to discontinue a study to move on to other research, determining what is an acceptable risk when making early health recommendations based on preliminary studies, the scientific community's initial incomplete understanding of the disease itself and the challenges of overburdened healthcare systems. Health Canada continues to work with domestic and international stakeholders to help accelerate the development and availability of drugs and vaccines that will prevent and treat COVID-19.

The book includes 10 chapters:

- History of Pandemics & Economics of COVID-19
- Public Health
- Comparison of International Jurisdictions
- Ethics
- Impact on the Healthcare Sector
- Governance and Operations
- Privacy and Security
- Liability and Litigation
- Research
- The Future after COVID-19

Reviewer

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