Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Reacting to crises: The COVID-19 impact on biostatistics/epidemiology

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ABSTRACT

Most crises, though difficult and challenging to address, offer opportunities for change and for development of new perspectives or approaches to deal with traditional strategies. The reaction to and the managing of the COVID-19 pandemic has provided a platform for evaluating how we quantify disease prevalence, incidence, time courses and sequellae as well as how well we plan, design, analyze and interpret health care associated data, including clinical trials and electronic medical records and health claims data. Whether the Covid-19 crisis provides opportunities to advance the fields of biostatistics and epidemiology in select ways remains to be seen. This article describes three areas of crises experienced by the author during a career in the regulation of pharmaceutical products and how they were responded to. Some suggestions for potential future opportunities in reaction to the Covid-19 crises are provided.

The impact of the covid-19 virus pandemic experience on virtually every aspect of current life has been transformative. It spans the tragic societal effects on morbidity and mortality, the societal disruptions brought about by the mitigation strategy of self - quarantining and social distancing, and the importance of a systematic and well-funded data collection infrastructure to support public health decisions and the data modeling that supports those decisions. Finally, we can ask what impact will this Covid-19 crisis have on the field of biostatistics/epidemiology. What the disciplines of biostatistics/epidemiology have to offer to the Covid-19 experience directly relates to the public's understanding of the need for and consequences of rigorous diagnostic testing, metrics of test accuracy, screening strategies, understanding basic statistical concepts such as rates of occurrence, statistical models based on daily counts of numerator cases however defined and associated mortality and statistical projections using compartmental and regression models and the often unaddressed topic of quantification of uncertainties associated with models and projections.

It occurred to me that crises of this sort, however unsettling, often stimulate new opportunities to advance methodologies, develop new clinical trial structures, create new initiatives that advance public health, and influence scientific disciplines, especially the fields of biostatistics and epidemiology. Crises are often sudden as is the Covid-19 pandemic but sometimes evolve more incrementally to a point where they must be dealt with. Having experienced several of these crises/events in my career at a regulatory agency, I thought it might be useful to revisit them from the perspective of what was learned from the events and what were the advances they stimulated. Finally, we might consider what the Covid-19 experience will impact and change in the future.

The crises / events and their impact that I will discuss are:

1) The AIDS crisis caused by the HIV virus escalated relatively quickly and had a tremendous impact on drug development, on the regulatory evaluation of evidence of treatment efficacy and safety, including on the design, conduct and analysis of clinical trials, on the creation of a clinical trials network to conduct trials of AIDS treatment, on statistical methods to understand and evaluate time dependent surrogate endpoints, and on the infusion of biostatistical talent into that infectious disease discipline, including both the FDA and the National Institutes of Health;

2) As a result of a successive series of life changing drug induced safety events in newly approved pharmaceutical drugs, usually called adverse events, many major changes occurred. The Congress passed new laws in the United States to address the issues, new clinical trial designs and approaches were developed to assess safety risks of new drugs, and a new national active drug surveillance system called the Sentinel System was created under the direction of the FDA in response to a Congressional mandate, which now is capable of monitoring electronic medical records of at least 150 million people in the US. This ushered in the new field of safety assessment of medical products;

3) With the increase in global drug development and the clinical trials conducted in many regions of the world by the pharmaceutical industry's drug development strategies, and with the need for both

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regulators from the United States, European Union and Japan to arrive at common standards for clinical studies so that foreign clinical data would be acceptable as evidence in all regulatory regions, a new international group known as the International Conference on Harmonization began in 1990. This was a reactionary effort of the pharmaceutical industry and regulators in the United States, European Union and Japan to meet a need that could evolve to a crisis but rather resulted in development of many internationally developed and consensus guidances to standardize practices and principles, in particular three guidances containing substantial statistical content, namely E9 on statistical principle in clinical trials, E5 on the acceptance of foreign clinical data and E17 on the multi-regional clinical trials. Each of these guidances has bearing on the clinical trials currently being planned or conducted on treatments and vaccines for the Covid-19 virus.

My focus in this article will be on how these experiences/events advanced the biostatistical and epidemiological communities and the clinical trial enterprise and pharmaceutical industry/regulatory environment in many ways. One might suggest that the Covid-19 virus experience will further add to future advances in each of these communities, particularly in the area of screening, surveillance methods and disease related surveys, statistical modeling and forecasting, innovative clinical trial designs for discovery of treatment strategies and confirmatory trials. Hopefully, we will see new improved infrastructures and increased resources that can deal with pandemics of this type in a more efficient manner.

1. The AIDS Crisis, the approval of the drug Azidothymidine (AZT), surrogate endpoints and clinical trial advances

Zidovudine (ZDV), also known as azidothymidine (AZT), is an antiretroviral medication used to prevent and treat HIV/AIDS [1]. It was the first drug approved to treat the disease and it changed the disease from a death sentence to one with successively better new treatment regimens alone and in combination. The clinical trial that was the basis of approval was published in the July 1987 issue of the New England Journal of Medicine but the story of its approval by the Food and Drug Administration (FDA) is worth discussing because both FDA and the National Institute of Allergy and Infectious Disease (NIAID) had to substantially change their infrastructure, their operating procedures and the clinical trial paradigm that existed at the time.

The clinical trial that was the basis of FDA approval to market the drug was sponsored by the NIAID and conducted by the pharmaceutical firm Burroughs–Wellcome. It was a double-blind, placebo-controlled trial of the efficacy of oral azidothymidine (AZT) in 282 patients with the acquired immunodeficiency syndrome (AIDS) manifested by *Pneumocystis carinii* pneumonia alone, or with advanced AIDS-related complex. The subjects were stratified according to numbers of T cells with CD4 surface markers and were randomly assigned to receive either 250 mg of AZT or placebo by mouth every four hours for a total of 24 weeks. One hundred forty-five subjects received AZT, and 137 received placebo.

While the clinical trial was ongoing, the incomplete interim mortality results and other information were made known to a limited group of representatives of NIAID and FDA (Center for Drugs and Biologics) in mid-March of 1987. The FDA representatives who would eventually be responsible to evaluate the study for approval, raised many questions about the study and the data that was available as there was considerable uncertainty about the status and completeness of the clinical outcomes of a subject in the trial and other aspects of the interim results, the data and the statistical analysis. Given the heightened interest and pressures for a first demonstrated effective therapy for AIDS (not different today for a Covid-19 treatment), FDA requested the sponsor to immediately conduct a full ascertainment of all investigators' patient outcomes and relevant follow-up information, so that a thorough statistical and clinical review of all current study data could be conducted. Within several days, FDA received all the relevant updated data which showed a doubling in the mortality count in the control group and 1 new death in the AZT group (bring the total to 18 to 1 in the control group and AZT group), and within a week completed its statistical and clinical evaluation of the study and announced approval of the drug. At the time it was unusual for FDA to conduct the study analyses and evaluate the veracity of the study conclusions.

What transpired next changed the infrastructures and some processes of both NIAID and FDA. NIAID hired a senior scientist Dr. Daniel Hoth from the National Cancer Institute who introduced and replicated the very successful cancer model of the cooperative study groups of ECOG and SWOG to NIAID. That was the beginning of the AIDS Clinical Trial Group network, called the ACTG, that still exists today and which has been the source of numerous clinical trials that have advanced AIDS treatments. The ACTG was established in 1987 to broaden the scope of the AIDS research effort of the NIAID. It supports the largest network of expert clinical and translational investigators and therapeutic clinical trials units in the world, including sites in resource-limited countries. These investigators and units serve as the major resource for HIV/AIDS research, treatment, care, and training/education in their communities.

As new clinical trials and protocols were rapidly being initiated by the pharmaceutical industry, NIAID and FDA then began to hold joint public meetings to discuss protocols and other aspects of AIDS study strategies, bringing AIDS activists into the discussion and changing the paradigm for how studies were being conducted. Many future clinical trials evaluated safer doses of AZT, combinations of treatments, use in earlier AIDS infected populations, mother to child transmissions, and the role of the CD4 counts and the viral load as clinical outcome worth longitudinal tracking. Finally, to shore up NIAID's statistical expertise for this clinical trial network, in 1988, Dr. Susan Ellenburg was hired from the National Cancer Institute to lead a biostatistics group in the Division of Aids in NIAID. These efforts transformed NIAID from a laboratory based research institute to one with a major clinical trial focus, and in the process facilitated and accelerated the education of a new AIDS clinical trial investigator community who had little experience at the time in planning and conducting clinical trials, especially those that would meet regulatory standards.

The FDA's Center for Drugs and Biologics (CDB) was itself substantially impacted by the AIDS crisis, and soon made structural changes to its drug review offices after the approval of AZT. What followed was the creation of a new Division of Anti-viral Drug products, under the leadership of Dr. Ellen Cooper, as well as an infusion of more biostatistical support for the surge of clinical trials that the pharmaceutical industry began to conduct. The pace of clinical development of new treatments alone and in combination increased dramatically.

At the same time, ongoing research and understanding of the epidemiology of AIDS evolved as the role of CD4 counts, viral load and other markers used as clinical trial entrance criteria and endpoints became better understood. Because FDA had access to all the current clinical trials of AIDS therapies ongoing at the time, the role of CD4 counts as a surrogate was evaluated for each trial. The interest in the surrogacy topic stimulated the major statistical movement to evaluate surrogate markers as an earlier predictor and substitute for AIDS related mortality as an endpoint in all clinical trials. The longitudinal paths of CD4 count changes in response to monotherapy and combination therapy received new attention, setting the stage for the seminal paper by Ross Prentice [2] on statistical criteria for surrogate markers. These criteria stimulated many researchers to initiate other research, resulting in new approaches and definitions to evaluate a full or partial surrogate endpoint [3–5] and also highlighted the use and role of meta-analysis of many studies to fully evaluate clinical endpoint surrogacy.

Soon to follow the approval of AZT was the creation of the regulatory process known as "accelerated approval on the basis of a surrogate endpoint", and that stimulated substantial public discussions at FDA's advisory committees on study designs, clinical endpoints, combination therapies, different optimal doses of treatments to minimize toxicity, the emphasis on viral load as an endpoint, the evaluation of mother to child

transmission and use of anti-virals to protect the child, etc. All of these changes were stimulated by the reaction to the AIDS crisis. One wonders what path of future drug development will follow from Covid-19 crisis.

2. The emergence of the science of safety assessment: large scale clinical safety studies and the active surveillance, Sentinel System

The next disruptive change to drug development and clinical trials came about in an incremental manner over a decade or so, as a series of public health safety issues in the form of drug adverse events associated with newly marketed drugs became more widely publicized and concerning to many. Eventually, the remedy was for the United States Congress to pass new laws with authorities given to US regulators to require pharmaceutical sponsors to conduct clinical safety studies pre-marketing as well as post-marketing to better assess and quantify risks of adverse events associated with new drugs. It is known that most late stage confirmatory clinical trials in drug development programs are designed to demonstrate the efficacy of a treatment and safety outcomes are usually not the primary focus nor are safety endpoints as thoroughly evaluated unless pre-specified in some manner. Safety endpoints may be unexpected and therefore more difficult to define in advance as with efficacy outcomes. The situation with regard to drug safety receiving less attention had been long standing and needed fixing. This began the new era of the science of safety assessment of new drugs, that required substantial biostatistical and epidemiologic expertise devoted to large outcome clinical trials designed to evaluate risk, and an increased investment in methods and approaches for observational data from electronic medical records, claims data and other health plan data sources. The field of pharmacoepidemiology in collaboration with biostatisticians was counted upon to advance the tools, methods and approaches to utilize real world data for active drug safety surveillance and risk assessment.

The following is a brief summary of some key events.

In the late 1990's, several weight reducing drugs, fenfluramine and dexfenfluramine, [6] were reported to be associated with cases of cardiovascular valvulopathy in women primarily. This caused considerable public health concerns as to the strength of evidence and veracity of the reports and the true causal mechanism since no clinical trial had been conducted to evaluate the risk. The drugs were withdrawn from the market. A few years later, the first anti-diabetic drug in its class, troglitazone (Rezulin) was found to have caused liver damage and was removed from the market. Following that incident, a drug rofecoxib, in the Cox-2 family of drugs used to treat various forms of arthritis and pain, was found to induce the major cardiovascular events of heart attacks and stroke, and it too was removed from the market [7] [8].

The adverse event experiences from these multiple marketed drug products resulted in initiatives that changed the landscape of safety assessment. Soon after rofecoxib had been withdrawn from the market in September 2004, hearings of the Senate Finance Committee and editorials in the lay and medical press raised serious questions about drug safety in the United States [9] .In response, the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) asked the Institute of Medicine (IOM) to assess the U.S. drug-safety system. The IOM assembled a diverse panel of experts who wrote a report that recommended sweeping changes to pre-and post- marketing safety assessment. This report stimulated congressional action that gave FDA new authorities to require clinical trials specifically designed to evaluate safety prior to market entry [9].

Finally, another newly approved anti-diabetic drug, rosiglitazone was reported to increase cardiovascular events and death in diabetic patients. These cardiovascular events associated with rosiglitazone were reported in a well publicized meta-analysis [10] whose results were widely debated and critiqued. In September 2010 the European Medicines Agency decided to suspend the market authorization of rosiglitazone, while the FDA decided to restrict the use of rosiglitazone. These actions were taken approximately 10 years after the introduction of rosiglitazone, because rosiglitazone might be associated with an increased risk of ischemic heart disease. This intense ongoing evaluation of the cardiovascular safety risks associated with anti-diabetes drug stimulated interest in the need for clinical trials to settle the issue. Following advice from one of its advisory committees, FDA issued in 2008 a guidance on clinical trials to address cardiovascular risks of new therapies for type 2 diabetes [11].

This guidance on assessment of cardiovascular risk of drugs to treat diabetes changed the design and planning for all future clinical trials devoted to large scale studies of safety outcomes not only for diabetes drugs but also obesity drugs and some arthritis / pain reducing drugs, New and unique design criteria never before applied, were introduced including statistical criteria for event driven clinical trials designed to achieve multiple objectives in a sequential manner, with the main design objective being ruling out a pre-specified increase in cardiovascular risk at two separate stage of development (80% 0r 20%), pre and post approval.

Over the next few years after the diabetes guidance was issued, a number of large studies specifically designed to meet these criteria were conducted at great cost, and they informed the public, the regulators and the pharmaceutical industry about the relative safety and benefits of these widely used classes of drugs. Recently, after reviewing the cardiovascular risk data from many completed studies that were informative about both the cardiovascular benefits as well as risks, FDA sought advice from its Endocrinologic and Metabolic Advisory Committee on the status of the 2008 guidance. The committee noted that safety data beyond ischemic cardiovascular safety data was also desired in order to evaluate the safety profile of antidiabetic drugs before they were approved. Accordingly, the initial draft guidance which focused only on cardiovascular risk was modified, the criteria was updated, dropping the pre-market criteria, and a new guidance informed by the results of completed safety studies was issued [12]. These incremental changes have strengthened the framework for systematic safety assessment with large safety clinical trials.

The series of adverse event crises just discussed stimulated yet another important regulatory initiative that was a reaction to many published meta-analyses of randomized clinical studies that alleged safety risks with approved drugs, including the rosiglitazone meta-analysis that was widely debated. These meta-analyses were often produced by academic scientists with no access to the raw patient level clinical data but rather only to summary statistics available in the published literature or even in the government data base ClinicalTrials.gov. Meta-analyses rest on substantial statistical methods that require professional statistical expertise to assess biases, appropriateness of the statistical methods, and assumptions for selection of the studies whose results are to be included in the meta-analysis. Usually, the studies included in these safety meta-analyses did not have safety outcomes as the primary objective of the clinical trial. Those studies included in the meta-analysis might have incomplete data follow-up for safety outcomes and lack other design induced relevant information about safety. This is especially true when relying on summary results derived from published literature for which the reporting of safety is often incomplete. Finally, it was not always clear if the protocol for the meta-analysis was written in advance of the study with pre-specified objectives or with sufficient detail to evaluate the selection criteria for the studies incorporated in the meta-analysis.

When these meta-analyses alleging a significant drug associated risk were published in the medical literature, they engendered considerable public concern and eventually it is the responsibility of FDA to adjudicate the finding and make public health decisions based upon the strength of evidence. FDA saw a need to place some principles in place to improve the evidentiary quality of these safety focused meta-analyses. Recognizing this as an increasing problem that regulators had to deal with, a draft guidance 'Use of Meta-Analysis of clinical trials for safety assessment.' was issued in 2019 [13, 14]. This is another example of

how crises stimulated by significant drug induced safety events stimulated change and new approaches to the use of clinical studies not designed for safety assessment.

The 2007 Food and Drug Amendment Acts requirement for clinical trials to study safety risks was not the only disruptive change to the science of safety assessment. The United States congress passed new legislation requiring FDA to develop a new massive active safety surveillance system that would complement the passive adverse event reporting system FAERS in the United States that had been in existence for decades.

Two impactful and groundbreaking projects were created to help FDA implement this congressional mandate [15].

One project was was the Observational Medical Outcomes Partnership (OMOP) which developed an approach to a collaborative network of researchers who could address a clinical safety /adverse event question using a common data model that allowed multiple stakeholders to be involved and contribute. OMOP was a public -private partnership involving the FDA, multiple pharmaceutical companies, and healthcare providers established to inform the appropriate use of observational healthcare data bases for studying the effects of medical products. A standard data model was developed and shared among the network of researchers. OMOP has evolved into a larger organization called The Observational Health Data Sciences and Informatics (OHDSI), whose goals, objectives and approaches can be seen on its website [www.ohdsi.org/wp-content/uploads/2019/11/OHDSI_1_Pager_v2.pdf]. OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University.

The second project supported by FDA began as a 5 year pilot program called Mini Sentinel which has matured to what is now known as the Sentinel System. Monitoring the safety of its regulated products is a major part of the FDA's mission to protect public health. Sentinel is the FDA's national electronic system which has transformed the way researchers monitor the safety of FDA-regulated medical products, including drugs, vaccines, biologics, and medical devices. In response to the FDA Amendments Act (FDAAA) of 2007, in May 2008 the FDA launched the Sentinel Initiative.[https://www.fda.gov/safety/fdas-sentinel-initiative]. The full Sentinel System officially launched in February 2016. Over time, Sentinel has developed the largest multisite distributed database in the world dedicated to medical product safety. It is constantly growing and improving to meet FDA's needs. Sentinel has published many important articles that help advance the use of electronic medical records and claims data for adverse event surveillance. Readers are encouraged to visit their website which contains substantial history and background as well as resources.

The Mini-Sentinel is a pilot program that is developing methods, tools, resources, policies, and procedures to facilitate the use of routinely collected electronic healthcare data to perform active surveillance of the safety of marketed medical products, including drugs, biologics, and medical devices. The U.S. Food and Drug Administration (FDA) initiated the program in 2009 as part of its Sentinel Initiative, in response to a Congressional mandate in the FDA Amendments Act of 2007.

After two years, Mini-Sentinel includes 31 academic and private organizations. It has developed policies, procedures, and technical specifications for developing and operating a secure distributed data system comprised of separate data sets that conform to a common data model covering enrollment, demographics, encounters, diagnoses, procedures, and ambulatory dispensing of prescription drugs. The distrib- uted data sets currently include administrative and claims data from 2000 to 2011 for over 300 million person-years, 2.4 billion encounters,

38 million inpatient hospitalizations, and 2.9 billion dispensings. Selected laboratory results and vital signs data recorded after 2005 are also available. There is an active data quality assessment and characterization program, and eligibility for medical care and pharmacy benefits is known. Systematic reviews of the literature have assessed the ability of administrative data to identify health outcomes of interest, and pro- cedures have been developed and tested to obtain, abstract, and adjudicate full-text medical records to validate coded diagnoses. Mini-Sentinel has also created a taxonomy of study designs and analytical approaches for many commonly occurring situations, and it is developing new statistical and epidemiologic methods to address certain gaps in analytic capabilities.

Assessments are performed by distributing computer programs that are executed locally by each data partner. The system is in active use by FDA, with the majority of assessments performed using customizable, reusable queries (programs). Prospective and retrospective assessments that use customized protocols are conducted as well. To date, several hundred unique programs have been distributed and executed.

Current activities include active surveillance of several drugs and vaccines, expansion of the population, enhancement of the common data model to include additional types of data from electronic health records and registries, development of new methodologic capabilities, and assessment of methods to identify and validate additional health outcomes of interesThe Mini-Sentinel was a pilot program to develop methods, tools, resources, policies, and procedures to facilitate the use of routinely collected electronic healthcare data to perform active surveillance of the safety of marketed medical products, including drugs, biologics, and medical devices. The U.S. Food and Drug Administration (FDA) initiated the program in 2009 as part of its Sentinel Initiative, in response to a Congressional mandate in the FDA Amendments Act of 2007. Mini-Sentinel included well over 50 academic and private organizations. It developed policies, procedures, and technical specifications for developing and operating a secure distributed data system comprised of separate data sets that conform to a common data model covering enrollment, demographics, encounters, diagnoses, procedures, and ambulatory dispensing of prescription drugs. Mini-Sentinel also created a taxonomy of study designs and analytical approaches for many commonly occurring situations, developed new statistical and epidemiologic methods to address certain gaps in analytic capabilities. Assessments are performed by distributing computer programs that are executed locally by each data partner. The system is in active use by FDA, with the majority of assessments performed using customizable, reusable queries (programs). Prospective and retrospective assessments that use customized protocols are conducted as well.

The Sentinel System[16] should enhance the ability to better utilize real world data for evidence and contribute to studies and surveillance of Covid-19 and its treatment strategies [17].

3. Efficiency in global drug development: International (ICH) collaboration to develop common standards for acceptance of clinical drug research – its impact on statistical practice

In the 1980's, as the pharmaceutical industry was increasing the conduct of clinical studies in many parts of the world, including Japan, Europe and North America, the regulators in those regions and the industry associations that represented the pharmaceutical industry recognized a real need. While the event was not sudden, and was not brought on by a pandemic, it was recognized as an urgent need to address the growing global crisis in drug development as it impacted public health in different regions of the world who might have to wait for effective therapies to reach them. Regulators and the pharmaceutical industry from these regions concluded that it was time to develop more consensus on common standards for drug and biologics development research so that duplicative programs would not be needed in different parts of the world and the cost of development could be made as efficient as possible so that patients would benefit from new drugs and biologics regardless of where clinical studies were conducted. While this initiative was not considered a crisis at the time, it was certainly a recognized major obstacle to the efficient development of safe and effective drugs, and adversely impacted public health and the patients waiting for new effective therapies.

In 1989, Europe, Japan, and the United States began plans for

harmonization. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created in April 1990 at a meeting in Brussels. ICH had the initial objective of coordinating the regulatory activities of the European, Japanese and United States regulatory bodies in consultation with the pharmaceutical trade associations from these regions, to discuss and agree upon the scientific aspects arising from product registration. Since the new millennium, ICH's attention has been directed towards extending the benefits of harmonization beyond the founding ICH regions.

In 2015, ICH underwent several reforms, and also expanded participation to other countries and regions of the world and changed its name to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use while becoming a legal entity in Switzerland as a non-profit association.

Since its beginning in 1990, many guidances have been developed in the areas of clinical studies, clinical practice, statistial principles for clinical trials, chemistry and manufacturing, drug safety and electronic standards. [see ICH website for full details and guidances, https://www.ich.org/].[18] Relevant to the biostatistical community is that statisticians representing regulators and the pharmaceutical industry associations from Japan, the United States and the European Union formed working groups tasked with the responsibility of developing guidance with substantial statistical content, something which had never been done before. Three important guidances have been developed that involve substantial statistical thinking which now influence statistical practices. The first and most impactful guidance essentially mandated that statistical expertise was expected as a critical component of clinical drug development, changing the international practice of statistics both in the regulatory and pharmaceutical industry. This seminal document was jointly developed by statisticians representing all the international regions and was titled E9 'Statistical principles for clinical trials". It was published globally in 1998 and has recently been updated in 2017 to address 'estimands' of treatment effects in clinical trials [see ICH E9(R). This update is intended to address,in part,the missing data problem in clinical trials that is well known and to set the stage for improving statistical practice globally.

Another ICH guidance E5 on 'Ethnic Factors in the Acceptability of Foreign Clinical Data was published in 1998, and in a follow-up Question and Answer Addendum published in 2006 introduced the concept of a multi-regional clinical trial to facilitate simultaneous entrance of new approved drugs into all ICH regions and to bridge trial results in one region to another. E5 provided a structure to view how heterogeneity of treatment effects can be influenced by intrinsic and extrinsic factors, a concept that is related to personalized medicine and characterizing the heterogeneity of treatment effects for different populations. The planning, design, analysis and interpretation of a multiregional clinical trial is a complex topic with many statistical issues that require substantial statistical insight and expertise for proper design and analysis. Because this topic was so complex and misunderstood, the ICH decided to authorize a new guidance specifically on the topic of multi-regional clinical trials as described in E5. This E17 guidance 'General Principles for Planning and Design of Multiregional Clinical Trials' was recently issued and is a major accomplishment that should also impact Covid-19 related clinical trials intended to demonstrate the efficacy and safety of treatments and vaccines that would be relevant for worldwide use.

These ICH guidances just discussed have substantial impact on the global development of new drugs and biologics, and especially on the practice of biostatistics and its discipline since virtually all biostatisticians in the drug and biologic development field know about them and have to adhere to the principles especially for clinical trials and for the acceptance of results of clinical studies conducted in regions outside of the local region.

A recent Covid-19 example of how extrinsic and intrinsic factors may impact the planning, design, analysis and interpretation of a multiregional clinical trial as described in the ICH E17 guidance was reported in the May 29,2020 issue of the Washington Post newspaper [article by Simon Denyer and Joel Achenbach] The concern expressed in the article was why the death rates per 100,000 people from Covid-19 differed so substantially among 15 countries ranging from Europe, North America, and Southeast Asia. These death rates ranged from 81/100000 in Belgium to 0.1 in Thailand and 0 in Vietman (data from Johns Hopkins University as of 5/26/2020). The various experts proposed that the differences might be due to very different interventions in some countries, including the wearing of masks and social distance and hand washing practices. Others suggested genes and the immune systems might be responsible since previous exposures to TB and Bacille Calmette-Guerin (BCG) vaccination may be causal factors. Other experts pointed out the dramatic difference in obesity of the populations which is a leading risk factor for serious Covid-19 illness ranging in prevalence from 36% in the US and 29% in Canada to 4% in Japan and India and 2% in Vietnam.

What these differences and/or disparities illustrate are the potential impact of both intrinsic and extrinsic factors, both of which should have to be planned for, measured and accounted for in any multi-regional clinical trial of covid-19 therapies.

4. Future contributions of biostatistics and epidemiology to manage the COVID-19 crisis

As many infectious disease experts expect Covid-19's impact to be felt for the foreseeable future absent vaccines and full containment, our current urgent situation should accelerate the collaborative involvement of biostatisticians and epidemiologists to apply best current methods and develop new methods and metrics for modeling the disease and its containment. As biostatisticians well know, the types and extent of predictions and most importantly the quantification of biases and uncertainties in our projections and estimates is critical, but not always appreciated, understood or requested by non-statisticians. The two major model approaches for Covid-19 disease modeling used to date, namely compartmental models and regression models are rapidly expanding and being researched by teams to include multiple time series, Markov processes, bias adjustment strategies and sensitivity analyses. Some of these approaches may contribute to improved methods of surveillance at national and local levels that rely upon networked data bases as the common data model approaches should also accelerate.

We are fortunate to have the Sentinel System in place that provides a national network of experts who adhere to common data models that allow pooling of data throughout the United States. In addition, the follow on organization to OMOP, the OHDSI also provides an important connected network of experts and data bases that should be useful in evaluating impacts of Covid-19. The Reagan -Udall Foundation has a website that is specifically devoted to advances and current information and initiatives for Covid-19 [see website and videos on the Covid-19 topic at https://reaganudall.org/]. In particular, the contributions of pharmacoepidemiologists, such as those involved over the last decade in advancing methodologies in various aspects of the Sentinel System, common data models that link various electronic health data base to create national networks of data sources should accelerate to meet modern health surveillance. However, data quality and data standards for electronic health records and claims data bases will need to simultaneously improve to maximize their utility and validity for decision making.

The interest in and emphasis on real world data and real world evidence for decision making sets the stage for supporting more informed management of Covid-19 related strategies and for more use of the Sentinel system for that purpose. The biostatistics and epidemiology communities should advance the causal analysis methodologies that already exist, but may have to build into such approaches the limitations of the data that is currently collected and its quality. As we seemed to have learned, the public's lack of appreciation for good quality data, for accurate estimates, for random sampling to obtain unbiased estimates of

important metrics is a huge challenge and will continue to be one of the educational challenges in the future if we are to advance the biostatistics/epidemiology contributions.

Given that the Covid-19 crisis is a pandemic, one would think that the infrastructure created by the International Council for Harmonization, with its guidances and emphasis on common standards, data quality, sound statistical planning and analysis methods, and good clinical practices for clinical trials should be an asset to get the global community moving on collaborative approaches. The principles that have been articulated in the ICH E17 guidance on multi-regional clinical trials, should have direct relevance to vaccine and treatment trials for Covid-19. One might ask if that organization will play a role in the future solutions to the crisis.

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