SCT Newsletter

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SCT Newsletter March 2019

Domenic J. Reda

Hello everyone,

Have you registered for the 40th Annual Meeting of the Society for Clinical Trials (May 19-22, 2019, New Orleans, LA)?

Just a few days left to take advantage of the early bird registration rates. March 31 is the last day you can register at this special rate. It looks like our new luncheon round-tables at the Monday lunch will be a success as a few of the round-tables have already reached capacity.

In this issue of our newsletter, we feature more of the exciting sessions the program committee has selected for the meeting. We honor our long-standing members, those who have had continuous membership in the Society for at least 15 years. Some of our members have held membership since the Society was formed!

You may also be interested in reading a recent announcement from FDA on their initiative to modernize clinical trials. One last thing, don't forget to make your hotel reservation at the 40th Annual Meeting conference hotel, the Sheraton New Orleans. You should register through the meeting web site to get the conference rate.

Domenic J. Reda,
SCT Secretary

Early Bird Rates Have Been Extended!

Early Bird Deadline is Now Sunday, March 31

40th Annual Meeting

of the Society for Clinical Trials

May 19 - May 22, 2019

New Orleans, LA

REGISTER NOW

SCT's 40th Annual Meeting:

"Clinical Trials: A Catalyst for Societal Advancement through Innovation"

The early response has been tremendous and this year's meeting is shaping up to be one of the best yet. The early bird deadline has been extended to March 31 to keep up the momentum. We hope we will see you in New Orleans!

Be sure to check out the schedule of events on the SCT webpage. You can click on any of the workshops or sessions to view the full abstract. The contributed sessions have now been added to the online program and can be reviewed here:

View Schedule of Events

Schedule subject to change

Round-Table Discussions are Filling Up Fast!

The SCT Meeting will be hosting round-table sessions focused on small group discussions and opportunities to be an involved SCT member during the Monday luncheon. Registration is required (at no cost) and are filling up fast. If there is a round-table which you would like to participate in which is currently full, please email sct@fernley.com to be added to the wait list.

Refer a Colleague to SCT!

In an effort to promote SCT membership within the current members' networks, the Membership Committee initiated a lottery for this year's annual meeting. Please consider referring a colleague or friend, especially in a field different from your own, who you think would benefit from SCT involvement. The meeting registration form will have a section for your referral to enter your name into the lottery. If you are selected, you will receive a gift card! The more referrals you have, the higher your chances of winning.

Learn more about SCT's 40th Annual Meeting

Hotel Accommodations Now Available

Sheraton New Orleans Hotel

New Orleans, LA

SCT standard room rate starts at $239 per night

Government rates available (with valid ID) starting at $161 per night

LEARN MORE >

Calendar of Upcoming Events

Event	Date/ Location	For More Information
SCT Society for Clinical Trials — **EARLY BIRD REGISTRATION DEADLINE**	**March 31** Midnight eastern time	REGISTER NOW
ICTMC 2019 5th International Clinical Trials Methodology Conference 6 – 9 October, Brighton, UK **Abstract Submission Deadline**	May 5, 2019	Click Here for Abstract Submission
SCT Society for Clinical Trials — **40th Annual Meeting**	May 19-22 New Orleans, LA	Click Here for Online PROGRAM
NIH/NINDS Clinical Trials Methodology Course	July 22-25 Iowa City, IA	Save the Date!
SCT Society for Clinical Trials — **41st Annual Meeting**	May 17-20, 2020 Baltimore, MD	Save the Date!
SCT Society for Clinical Trials — **42nd Annual Meeting**	May 16-19, 2021 Chicago, IL	Save the Date!

40th Annual Meeting: Keynote Speakers

Dr. Thomas Fleming

Curtis Meinert Keynote

Monday, May 20 at 8:00 AM ET

Dr. Thomas Fleming
"Striving to Achieve and Protect the Integrity of Clinical Trials"

Dr. Monica Bertagnolli

Founders Lecture Keynote

Tuesday, May 21 at 8:00 AM ET

Dr. Monica Bertagnolli:
"Building a Learning Health Care System, and Learning from Every Patient"

Featured Sessions at the 40th Annual Meeting

By Letitia Perdue, Program Committee Chair

The Annual Meeting is fast approaching and we are excited to highlight some of the sessions scheduled for the second day of the meeting. You can find the full program on the meeting page of the SCT website.

You won't want to miss the Special Founders Session on Tuesday, May 21 at 5:00 pm where we will recognize and honor the Founders of the Society.

Founders of the Society for Clinical Trials, Inc.

Organizer/Chair:	KyungMann Kim, University of Wisconsin-Madison
Speakers:	O. Dale Williams, Retired
	Barbara Hawkins, Johns Hopkins University
	John M. Lachin, George Washington University
	Elizabeth Wright, National Institutes of Health
	Theodore Karrison, University of Chicago
	Domenic Reda, VA Hines CSP Coordinating Center

The Society for Clinical Trials, Inc. was incorporated on September 22, 1978 in the State of Maryland's State Department of Assessments and Taxation with the following Board of Directors: Thomas C. Chalmers, MD, Harold O. Conn, MD, Fred Ederer, MS, Robert S. Gordon, Jr. MD, Christian R. Klimt, MD, Paul Meier, PhD, Curtis L. Meinert, PhD, Charles Moertel, MD, Thaddeus Prout, MD, Harold P. Roth, MD and O. Dale Williams, PhD, i.e. the Founders of the Society. It is noteworthy that the Founders included four statisticians and seven physicians. The Society was "organized and formed for charitable, educational and scientific purposes and not for pecuniary profit or financial gain" and "exempt from Federal income tax under Section 501(c)(3) of the Internal Revenue Code." Upon the 40th annual meeting of the SCT, it seems befitting to recognize and honor them. The objectives of the session are to learn about the Founders and their motivations behind the foundation of the Society 40 years ago, to take stock of what the Society has accomplished since its foundation in 1978, and to envision the future of the Society beyond its first 40 years. Speakers of the session have personal knowledge of or worked closely with the Founders, and will share their first-hand account of the Founders, their own recollections about the Society, and their vision for the future of the Society.

Other invited sessions happening on Tuesday include:

SAFEGUARDING PUBLIC AND PATIENT TRUST IN PRAGMATIC TRIALS WITHOUT WRITTEN INFORMED CONSENT

There is a growing interest among researcher funders, policy-makers, investigators, and healthcare providers in conducting pragmatic clinical trials—that is, trials designed to more directly address the knowledge gaps in clinical practice. However, for some kinds of pragmatic trials, the traditional process of collecting formal, written consent from all research subjects may be impossible, impracticable, or pose a threat to the validity of the study. Yet because written informed consent has been one of the primary means of operationalizing the ethical principle of respect for persons, conducting trials without written consent may pose a threat to public and patient trust in research.

In this hybrid invited/panel session, our first speakers will provide an overview of the ethical challenges for patient and public trust in research around the issue of informed consent, as well as presenting a concrete example of a pragmatic trial without written consent that is currently underway at the Ottawa Hospital Research Institute. These talks will then be followed by a panel discussion (with the audience) on the various scientific, ethical, and legal issues at play.

Introduction: This brief presentation will orient the audience to the motivating question, introduce the speakers and panelists, and lay out the plan for the session.

What is the evidence for patient and public trust in research? Despite the fact that preserving patient and public trust is one of the cornerstone principles of the research ethics, there is remarkably little empirical work evaluating whether patients and the public believe that their interests are being protected or promoted by the research enterprise. In this presentation, Dr. Brehaut will review some of the empirical literature on this topic, highlighting variance in levels of trust and specific issues to target for improvement.

Patient-reported measures of informed consent. There are currently an array of different tools used to assess the informed consent process. While some validated measures do exist, it is not clear that these tools all measure informed consent in the same way. It is also not known whether they measure aspects of informed consent that actually matter to potential trial participants. In this talk, Dr. Gillies will address these issues by outlining findings from a review of validated measures of informed consent for clinical trials and present preliminary evidence from interviews with trial participants (and other key stakeholders) about what they deem important to judge whether the informed consent process went well.

Description of iTAD study. There is growing pre-clinical and clinical evidence that characteristics of blood donors may affect transfusion recipient outcomes. In this presentation, Dr. Fergusson will present on his experience designing and initiating the innovative Trial Assessing Donor Sex on Recipient Mortality (iTADS), a multi-center, pragmatic, randomized controlled trial to test the effect of donor sex on transfusion outcomes. In particular, this talk will focus on the decision to not use written informed consent, and how this decision was negotiated with the trial's research ethics board.

Panel discussion. The panel portion of the session will feature a diversity of perspectives on the topic. It will then transition to a Q&A discussion among all the panelists and the audience,

SYNTHESIZE READ-WORLD DATA WITH RANDOMIZED CLINICAL TRIAL DATA FOR EFFICIENT DRUG DEVELOPMENT

Data from “real world” clinical practice and drug utilization – outside of clinical trials – is regarded as a pragmatic source of evidence with high potential to support clinical development and life cycle management of medical products. Both US and EU regulatory agencies, public-private partnerships and health technology assessment organizations have launched major initiatives to address issues regarding the use of real world data (RWD) to inform regulatory decision making. In PDUFA VI, the FDA has committed to explore enhancing use of RWD in regulatory decision making, to hold public workshops, and to publish draft guidance documents between 2018 and 2021. Robust RWD will not only leverage increasing volumes of data, but weave together different sources of data, such as clinical data, registries, and electronic health records, to bridge the gap between efficacy and effectiveness and enhance the efficiency of drug development. Although many challenges and limitations remain with the use of RWD, there have also been many successful case studies. In this session, speakers from academia, industry, a research organization and the FDA will discuss the opportunities and challenges when synthesizing real-world data and randomized clinical trials data to generate comprehensive evidence packages to facilitate more efficient drug development and inform regulatory decision-making. Issues such as the selection of appropriate cases for regulatory considerations, data availability and what constitutes substantial evidence in the real-world setting will be discussed. Examples on using RWD to design randomized clinical trials and a case study will be shared.

Speakers and Presentation Titles:

Cathy Critchlow, PhD, Vice President, Center for Observational Research, Amgen, ccritchl@amgen.com; Title: Evolving Role for Real World Evidence to Inform Regulatory Decision-making

Frank Rockhold, PhD, Professor of Biostatistics and Bioinformatics, Duke Clinical Research Institute, frank.rockhold@duke.edu Title: The Randomized Pragmatic Trials Journey: Myths and Realities

Zhaoling Meng, PhD, Head of Statistical Methods and Clinical Trial Simulation, Bill & Melinda Gates Medical Research Institute, zhaoling.meng@gatesmri.org Title: Real World Evidence and Model-Informed Drug Development – an Antidiabetic Drug Cardiovascular Outcome Case Study

Martin Ho, PhD, Associate Director for Quantitative Innovations, FDA, Martin.Ho@fda.hhs.gov Title: Using RWD to Design Clinical Studies: a Regulatory Perspective

CHALLENGES IN DESIGN, ANALYSIS AND SELECTION OF ENDPOINTS IN IMMUNO-ONCOLOGY TRIALS

The novel mechanism of action (MOA) of immunotherapy agents, in treatment of various types of cancer, poses unique challenges during the design and analysis of clinical trials. This is often reflected in the clinical data when analyzing time to event endpoints such as progression free survival (PFS) and overall survival (OS), where we observe Kaplan Meier (KM) curves that separate after a long time (or may initially be in favor of the control arm but eventually cross in favor of the experimental arm). A plateau observed at the tail of the curve with longer follow-up is common as well, reflecting potential long-term benefit on some patients treated with these new agents. There is also less clarity on clinical endpoints that best captures treatment benefit of these agents. Often, at an individual patient level, achieving a tumor response or long term stable disease is a very good indicator of prolonged OS. However, at the trial level, lack of benefit in objective response rate (ORR) or PFS may not necessarily predict for lack of OS benefit.

In this session, we focus on two important challenges in the design and analysis of immune-oncology (IO) trials. 1. Evaluating statistical methods that better help design our trials and interpret results when the PH assumption is violated. 2. Understanding the relationship between ORR, PFS and OS, which can better guide in decision making both at the individual patient level and the trial level.

Under the traditional paradigm of designing of clinical trials with time to event endpoints, PH assumption is commonly used. However, the presence of non-proportional hazards (NPH) treatment effect has been well documented in the context of IO studies, where a delayed separation of the Kaplan-Meier (KM) curves have often been observed. Other more complex forms of NPH, such as crossing KM curves are also seen in practice, making analytical approaches and interpretation of study results, more challenging. In these cases, summarizing the treatment effect based on hazard ratio alone may not be informative. Hypothesis testing with log-rank test and clinical trials designed based on proportional hazard assumptions are likely to be underpowered to detect treatment differences.

A cooperative effort with the Pharmaceutical Industry was initiated by the FDA in late 2016 to take a holistic approach in understanding the impact of NPH in the design, analysis and interpretation of clinical trials. In identifying new methods for analyzing time-to-event data, the cross-pharma working group examined widely used methods for hypothesis testing and estimation in the presence of NPH, such as log-rank based tests, restricted mean survival time, and the piecewise Cox model. They determined that a new method was needed to analyze these time-to-event data and have proposed a new combination test based on Fleming-Harrington weighted log-rank statistics. The proposed methodology provides robust inference for a large class of NPH scenarios of interest.

In this session, we follow the recommendations from the working group, and evaluate the performance of the weighted longrank tests and the combination test under various NPH scenarios, with a focus on the scenario of crossing KM curves. Both simulations and case studies are used to understand the properties of these tests. The clinical interpretation of results in the presence of such NPH are discussed, taking into consideration probable underlying causes for the NPH.

Unlike in the chemotherapy and small molecule setting, the relationship between traditional tumor based endpoints such as ORR and PFS with OS and the impact of IO agents on these endpoints, both at the trial level, as well as the individual patient level, is less clear. We evaluate the relationship between treatment effects of PFS or ORR with that of OS using available trial level data from randomized studies across multiple solid tumors, reported in the literature. We also explore the correlation between these endpoints at the individual patient level, using datasets from advanced solid tumors. Understanding these relationships can better help in endpoint selection and also in developing appropriate go/no go thresholds for proof of concept studies.

We will evaluate these two problems using several case studies and patient level datasets to provide pragmatic solutions for the design and analysis of IO trials, as well as choice of endpoints that can better guide decision making. We will also discuss how the current regulatory and reimbursement landscape is evolving in this regard and opportunities for collaboration with regulators and payers in driving the science forward.

Dr. Mukhopadhyay and Dr. Anderson will co-chair this session. Dr. Roychoudhury and Dr. Anderson will individually present on the work done as part of the cross-PhRMA working group looking at issues with NPH and proposed solutions during design and analysis of IO trials. Dr. Mukhopadhyay will discuss relationship between ORR, PFS and OS using trial level and patient level data in patients treated with anti-PD1/PD-L1 agents in advanced solid tumors. Dr. Halabi, who is a professor of statistics at Duke University, will provide insights on the above topics from an academic perspective highlighting areas of collaboration between industry and academia Dr. Abdullah, who is the head of IO Clinical development in Astrazeneca will provide clinical and regulatory insights on these topics and discuss where the field is evolving in terms of the clinical research and the regulatory/payer landscape.

DIVERSE REPRESENTATION IN CLINICAL TRIALS

Despite public expectations, regulatory directives, and widespread interest within industry and academia, the composition many clinical trials do not reflect the diversity of the population at large or those likely to use the investigational product. Historical under-represented groups remain understudied, and variability in treatment response and tolerability go undetected. Considerable data support the scientific and social value of inclusiveness in enrollment such that the role of factors like sex, gender, race, ethnicity, age, and sociodemographic factors can be examined. The panel brings together leaders from government, industry, and academia to discuss their unique perspectives on impediments to diversify trials. The session will propose and discuss actionable and scalable solutions to address impediments at the level of trial development and implementation to promote the goal of diversity in enrollment and to facilitate necessary subgroup analysis in clinical trials.

Panelists include representatives from industry (Dr. Luther Clark, Merck, panelist), academia (Dr. Barbara Bierer, Harvard Medical School, panelist; Dr. David Strauss, Austen Riggs Center, moderator), and government (CAPT Richardae Araojo, FDA, panelist). They will present data explaining why diversity is essential for successful clinical trials and discuss the systemic deficiencies within the clinical research

landscape faced by patients, clinical research organizations and sponsors. One of the panelists will focus on the barriers around the inclusion and exclusion criteria of protocols in clinical trials and proposed recommendations. The second panelist will examine the challenges around financial and time costs associated with stakeholders, and issues regarding data collection and analysis. The third panelist will discuss and share innovative approaches, 'tools', and implementation frameworks that can be applied by different stakeholders to realize the potential of having diverse participants.

SCT Membership Committee: 2018-2019

Jody D. Ciolino, PhD
Dixie J. Ecklund, RN, MSN, MBA, CCRC

Who are we?
The SCT Membership Committee is comprised of two co-chairs (Jody Ciolino and Dixie Ecklund) and seven additional active members.

Name	Institution	Primary Field
Co-chairs		
Jody D. Ciolino, PhD	Biostatistics Collaboration Center, Northwestern University	Biostatistics
Dixie J. Ecklund, RN, MSN, MBA, CCRC	Clinical Trials Statistical & Data Management Center, Director of Operations, University of Iowa	Clinical trials, data management, project management, protection of human subjects
Members:		
Jodi DeStefano	EMMES Corporation	Clinical Systems, Electronic Data Capture / Platform Development
Kimberly Drews, PhD	George Washington University	Biostatistics
Kathleen A. Jablonski, PhD	George Washington University	Epidemiology
Julie Qidwai, MS, CCRC	University of Iowa	Clinical Trial Coordination
Ellen R. Rosenberg, MA	National Institutes of Health	Clinical Research Project Manager
Dikla (Dee) Shmueli-Blumberg, PhD	EMMES Corporation	Clinical Coordinating Center, Psychology
Maggie K. Spencer, MA	University of Iowa	Research Administration

What do we do?
The primary goals of the membership committee are to: (1) increase and sustain membership for SCT; (2) increase membership diversity, including diversity across fields represented within the Society; and (3) increase collaboration between SCT committees.

Since the 2018 annual meeting, the Membership Committee activities have increased from previous years as we work with Fernley & Fernley, Inc. staff to monitor membership size and distribution and propose initiatives to the SCT Board in an effort to achieve our goals. We have held monthly teleconferences to brainstorm, work on initiatives, develop action items, and provide updates. These discussions uncovered two key findings: (1) there is a need for additional collaboration across the several committees within the Society (e.g., Education, Program, Communications, etc.), and (2) the majority of the membership base identifies biostatistics / statistics as its primary field.

As a result of these findings, the Membership Committee initiated a plan to have scheduled updates involving leadership representation from all SCT committees. We plan to continue to work more closely with the Communications Committee and Social Media Sub-Committee in an effort to boost advertisement for the Society. Members of the committee have also circulated vetted announcements to their individual collaborative networks, including Clinical and Translational Science Award (CTSA) institutions and through social media – both personal and professional accounts. As fellow members, we ask that you please consider promoting the Society through your own networks (Twitter: @SCTorg; use #SCT2019 for the annual meeting).

Refer a colleague or friend to SCT

You may have seen a recent newsletter advertise a lottery for this year's annual meeting. In an effort to promote SCT membership and increase membership diversity, the Membership Committee is asking all SCT members to consider referring a colleague or friend to this year's meeting. The meeting registration form has a section for your referral to enter your name into the lottery. If you are selected, you will receive a gift card! The more referrals you have, the higher your chances of winning.

Why are we doing this?

We hope that the efforts of the committee will both increase continuity and cohesion within the Society, and increase diversity of fields represented. It is our thought that while biostatistics / statistics are imperative to the field of clinical trials, without representation from the other fields such as: data management, clinical systems, nursing, project management, ethics, regulatory guidance, clinical experts, etc., clinical trials are impossible. Any clinical trial, no matter the size or phase is a multidisciplinary team effort.

Further, increasing and sustaining the membership for SCT to ensure the Society thrives will allow for continued success in training current and future clinical trialists. This Society not only allows a professional development platform for anyone involved or interested in clinical trials, but it provides an avenue for sharing of best practices, methods, and rigor and reproducibility to help move the field of clinical trials-and all those encompassed within it-forward.

What's next?

As we approach the annual meeting in New Orleans (May 19-22, 2019), we will continue to monitor our membership numbers and field representation. We are working with the SCT Leadership to formalize procedures and policies within the Committee(s) and ensure increased momentum and continuity for year(s) to come. We welcome any other Society members interested in sharing ideas and becoming a part of the SCT Membership Committee to contact jody.ciolino@northwestern.edu.

SCT Honors It's Long-Standing Members

The Society for Clinical Trials was founded in 1978. Among current members, we have people who have held continuous membership since 1979! SCT would like to thank these distinguished and faithful members for their support of the Society. If your name is not listed below and you believe it should be, please contact our management office at sct@fernley.com.

35+ Years	30-34 Years	25-29 Years
Barry R. Davis	Raymond P. Bain	Beverley Adams Huet
David L. DeMets	Gerald Beck	Colin B. Begg
Marie Diener-West	Roy W. Beck	Jeff F. Doerzbacher
Dennis O. Dixon	Jesse A. Berlin	Robert G. Edson
Susan S. Ellenberg	Mark Espeland	Ciro Gallo
Sandra A. Forman	KyungMann Kim	Richard Goldstein
Barbara S. Hawkins	Maureen Maguire	J. Terrell Hoffeld
James E. Herndon, II	Gordon D. Murray	Michael D. Hughes
Jay Herson	Paula K. Roberson	Edward Lakatos
Virginia J. Howard		J. Jack Lee
Gary R. Johnson		Anne S. Lindblad
John M. Lachin		Eleanor McFadden
Jeannette Lee		Michael E. Miller
Kelvin K. Lee		David C. Musch
Philip C. Prorok		James D. Neaton
Domenic J. Reda		Elinor Randi Schoenfeld
Frank W. Rockhold		Wasima N. Rida
Kenneth Schechtman		Anne Ryan
Stan Shapiro		Ji Zhang
Janet Wittes		
Elizabeth C. Wright		

20-24 Years	15-19 Years	15-19 Years Cont'd
Steve Belle	Judith M. Bliss	Elizabeth Ludington
Neil M. Bressler	Marion Campbell	Yutaka Matsuyama
Nicole C. Close	Douglass Chapman	Leslie Ain McClure
James J. Dignam	Dana Creanga	Wendy R. Parulekar
Scott R. Evans	Simon Day	Elaine Pascoe
Virginia Filiaci	J. Michael Dean	Marc Schwartz
Richard D. Gelber	Lori Dolan	Jonathan R. Smith
Stephen L. George	Kirk Easley	Satoshi Teramukai
Susan Groshen	John C. Evans	Sven Trelle
Daniel F. Heitjan	Katherine A. Guthrie	Lehana Thabane
Leslie A. Kalish	Susan Halabi	Paul G. Wakim
Laura Lovato	Toshimitsu Hamasaki	Marc Walton
Michele Melia	Wei-Ting Hwang	Zi-Fan Yu
Carol K. Redmond	Masha Kocherginsky	
Jay P. Siegel		
James C. Torner		

FDA Announcement

March 14, 2019:
Statement by FDA Commissioner Scott Gottlieb, M.D., on new strategies to modernize clinical trials to advance precision medicine, patient protections and more efficient product development

The following announcement is shared via the FDA Website:

Statement:

Modernizing clinical trials is an agency wide priority. As more diseases are being redefined based on genomic subtype, researchers have more novel targets and more opportunities to precisely modulate or even repair the basic biological drivers of illness. Precision guided medicines can demonstrate strong efficacy signals in early clinical trials, including in trials where small groups of patients are selected based on biomarkers or other criteria suggesting they're likely to benefit. These trials can potentially allow earlier regulatory assessment of benefit and risk. When the agency can make a positive approval decision, patients can gain earlier access to important new therapeutic options. To take advantage of these innovations, the agency is also seeking new ways to modernize its approaches to accommodate these novel opportunities.

The FDA isn't alone. The advent of precision medicine is challenging the entire medical research ecosystem to develop more efficient approaches to testing and developing diagnostics and therapeutics, to harness the full potential of science to reduce the suffering, death, and disability caused by complex human illnesses. The agency is committed to developing a regulatory framework for precision medicine that generates robust evidence of product safety and efficacy as efficiently as possible, including frameworks that are more carefully suited to the kinds of precision technologies that underpin new treatments.

But these opportunities can be delayed or stymied by a clinical research enterprise that is often extraordinarily complex and expensive. Efforts to streamline medical product development based on advancing science can be frustrated by legacy business models that discourage collaboration and data sharing, and the adoption of disruptive technologies that make clinical research more effective. Without a more agile clinical research enterprise capable of testing more therapies or combinations of therapies against an expanding array of targets more efficiently and at lower total cost, important therapeutic opportunities may be delayed or discarded because we can't afford to run trials needed to validate them.

The agency has worked closely with stakeholders, including the Clinical Trial Transformation Initiative, to identify innovative trial designs, evaluate the role of decentralized clinical trials and mobile technologies, and help validate novel endpoints that can enable trials to generate reliable evidence needed to assess product safety and efficacy more efficiently. For instance, the FDA has pioneered master protocol trial designs that can evaluate, in parallel, different drugs compared to their respective controls or to a single common control. These trials can be updated to incorporate new scientific information, like novel biomarkers, as medical science advances. The infrastructure for these

trials can last for decades. This reduces administrative costs and time associated with standing up new trial sites for each drug candidate.

Unfortunately, we've seen a continued reluctance to adopt innovative approaches among sponsors and clinical research organizations. In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive but disruptive changes that certain innovations can enable. We appreciate that scientific and technical complexity is a real and ongoing challenge, but industry and academia also need to invest in and leverage these approaches and develop new incentives that reward collaboration and data sharing across the clinical research enterprise.

New research paradigms are needed to break down barriers between real world data and clinical research, so that evidence can be shared rapidly to improve both domains across a learning health care system. For instance, more trials can incorporate data from electronic health records, and adopt electronic informed consent, to enroll more patients in clinical trials closer to where they live and work. This can reduce barriers to clinical trial participation and accelerate researchers' ability to ask and answer important questions.

We're committed to advancing more of these approaches through additional guidance and workshops that we're announcing that are focused on overcoming bottlenecks to modernizing trial infrastructure.

This week, we released guidance for sponsors on how they can incorporate patients with more challenging health conditions into oncology clinical trials. This includes patients with brain metastases or previous malignancies; patients with organ dysfunctions, as well as adolescent and pediatric patients. Inclusion of these patients can make trials more representative of real world oncology care.

Today, we're releasing additional guidance for industry on strategies that can support the development of precision medicines, and guidance on risk-based monitoring that can be accomplished through the incorporation of more computerized systems for effective oversight. These guidances, Enrichment Strategies for Clinical Trials to Support Determinations of Effectiveness of Human Drugs and Biological Products, and A Risk Based Approach to Monitoring of Clinical Investigations: Questions and Answers Guidance for Industry, can help facilitate efficient development of novel innovations, while also generating the robust evidence needed to better assess product safety and efficacy.

We're also releasing a final guidance for industry, Severely Debilitating or Life Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals (SDLTHDs). This guidance is intended to streamline the development of pharmaceuticals used to treat patients with SDLTHDs, other than cancer, while protecting patients' safety and avoiding unnecessary use of animals in the conduct of trials.

The guidance addresses the appropriate use of non-clinical tests, both in vitro and in animal models. These approaches can facilitate streamlined development programs by improving sponsors' understanding of drug or biologic effects on biological pathways, or potential organ toxicity, while still protecting patients' safety and avoiding unnecessary use of animals. These methods are in accordance with the 3Rs (reduce, refine, replace) -- principles that govern the proper conduct of non-clinical research and that the FDA supports. Non-clinical evaluations include pharmacology, safety pharmacology, general toxicology, genotoxicity, reproductive toxicology, carcinogenicity, immunotoxicity, photosafety testing and pharmacokinetics.

This guidance applies to drugs used both to treat the active disease and to prevent the recurrence of a life-threatening or debilitating event. Some examples of SDLTHDs are multicentric Castleman's disease, aplastic anemia, paroxysmal nocturnal hemoglobinuria, hemophilia and sickle cell disease.

Enriched Trials

Enrichment is also a key strategy in the development of precision medicine. Under these approaches, treatments are targeted at groups of patients based on clinical laboratory tests, genomic or proteomic factors. Enrichment strategies rely on the selection of patients for clinical trials based on one or more characteristics intended to demonstrate the safety and/or effectiveness of the drug or biologic in selected populations. Enrichment can make it easier to detect a drug's effect (if one is present) in a biomarker selected population – for instance, HER2 Neu+ positive breast cancer - than it would be in a larger population that hasn't been prespecified, and where only a select population of patients would respond.

These approaches can allow signal detection in smaller clinical trials, or trials of shorter duration, compared to ones that are open to "all comers." For instance, when the high-responder population constitutes only a small fraction of all patients, such as 20 percent (a common situation in oncology settings), enrichment may generate evidence of effectiveness in a small study, including only potential responders, when showing any effect in an unselected population where only 20 percent could respond would be much more difficult. The information gleaned from these approaches can also guide clinical practice, to help doctors get the right treatment to the right patient at the right time. The same information used to select patients based on their likelihood of responding positively to a drug in a trial can be used to guide real world care.

The guidance we're issuing today, Enrichment Strategies for Clinical Trials to Support Determinations of Effectiveness of Human Drugs and Biological Products, can help expand the use of these approaches and facilitate development of innovative enrichment strategies in tandem with advancing science.

Risk Based Monitoring

Protecting human subjects in trials is another critical part of the FDA's mission. Sponsors of clinical investigations involving human drugs, biological products, medical devices, and combinations thereof are required to provide oversight to ensure adequate protection of the rights, welfare and safety of human subjects and the quality of the data submitted to the FDA. The regulations are not specific about how sponsors are to conduct such monitoring; a range of approaches to monitoring are compatible with the regulations.

Traditional on-site monitoring of each clinical site to evaluate study conduct and perform 100 percent source data verification is highly resource intensive and may account for up to a third of the total clinical trial cost. But traditional on-site monitoring that is overly focused on source data verification doesn't guarantee data quality.

Risk-based monitoring, as a component of a sponsor's overarching quality risk-management systems and trial-specific quality by design programs, can help to provide more efficient oversight of trials, while still protecting human subjects and assuring data integrity. To support greater use of efficient risk-based monitoring, today's guidance on A Risk-Based Approach to monitoring of Clinical Investigations: Questions and Answers provides guidance to industry on implementing risk-based monitoring of

investigational studies of human drug and biological products, medical devices, or drug and device combinations.

This guidance can help sponsors tailor monitoring plans to the needs of the clinical investigation, while focusing on those risks that have the greatest potential to adversely affect study quality, including critical risks to the maintenance of the rights, safety, and welfare of trial participants, and the collection and analysis of key safety and efficacy endpoint data. Risk based monitoring can be advanced using computerized algorithms that enable remote and central trial monitoring, as well as the development of advanced analytics that can be used to monitor data integrity as a trial is in process.

We look forward to working with our many stakeholders to support the development of these modern approaches and make the promise of precision medicine a reality for more patients.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

All content is via the FDA website:

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633500.htm?utm_campaign=031419_Statement_FDA%20issues%20statement%20on%20new%20strategies%20to%20modernize%20clinical%20trials&utm_medium=email&utm_source=Eloqua

National Institutes of Health
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Extramural Nexus

Excerpts from March 2019 Edition

Full Text

Open Mike

Update on NIH's Efforts to Address Sexual Harassment in Science

By **Mike Lauer**

Today we released a very important statement outlining actions NIH is taking to become part of the solution to address sexual harassment in science. I am including the full text of the statement below, as it speaks for itself. For additional information please visit our webpage. Continue reading →

Seeking Input on the Need to Enhance Access to NIH Grants Data

By **Mike Lauer**

NIH has long been committed to transparency into who and what we fund. We have previously discussed the value of freely-available web tools that allow you to gain insight into NIH funding decisions. Award data available via RePORT and RePORTER, for instance, include non-sensitive information such as awardee institution, principal investigator, funding levels, research abstracts, as well as associated publications, patents, and other project outcomes. The data available through RePORT are quite powerful in their own right. However, compelling arguments exist for why researchers outside NIH should have access to even more information associated with the grants process. Continue reading →

Top Stories

Uploading Studies to ClinicalTrials.gov Just Got Easier

When conducting clinical trials, NIH funding recipients are required to register their study at ClinicalTrials.gov. To make registration easier, a new feature in the eRA Human Subjects System (HSS) allows applicants and recipients to export study record entries as an XML file, and upload fields that are captured in both systems directly into ClinicalTrials.gov's Protocol Registration and Results System (PRS). Continue reading →

HTMR newsletter

MRC Hubs for Trials Methodology Research

www.methodologyhubs.mrc.ac.uk

From the March 2019 Edition:
Funding News: Trials Methodology Research Partnership

In case you missed our announcement late last year, the MRC HTMR Network is delighted to announce that the Trials Methodology Research Partnership funding application, which was submitted to the MRC-NIHR Methodology Research Programme in June, has been successful.

The Trials Methodology Research Partnership (TMRP) will bring together a number of networks, institutions and partners working in trials and trials methodology research.

At present, the partner networks who will join the five Hubs within the MRC HTMR Network include the Global Health Network (TGHN), Health Research Board Trials Methodology Research Network (HRB-TMRN) , Health Data Research UK, the UKCRC Registered CTU Network and the UK Trial Managers' Network (UK TMN). In addition, groups from 21 universities are collaborating to offer doctoral training in trials methodology research to a new cohort of students (Aberdeen, Bangor, Birmingham, Cardiff, Edinburgh, Exeter, Glasgow, King's, Lancaster, Leeds, Liverpool, LSTM, Manchester, MRC BSU, MRC CTU, Newcastle, Nottingham, Oxford, QMUL, Sheffield, York).

Professor Paula Williamson, current HTMR Network Chair and Lead for the new partnership, commented "Our vision is to foster an environment which attracts the very best trials methodologists, both as staff, students and collaborators, working in areas of high priority and with key stakeholder groups to exert influence and achieve impact. Our overall aim being to improve patient care by improving the way in which the healthcare evidence base is developed."

The TMRP offers an opportunity to build on the achievements of the MRC HTMR Network while exploring new collaborations and avenues to make continued progress in advancing trial methodology, developing capacity and further reducing research waste. The Partnership will be launched May 2019.