DEAR COLLEAGUES:

As we usher in a new era for research, development, and implementation, we reflect on the past 25 years of the DCRI Think Tank series and what it has represented: the opportunity to collaboratively define how it should be done.

The COVID-19 pandemic has undeniably posed challenges, but it has also allowed us to think creatively and try new approaches. We successfully pivoted to virtual Think Tank meetings, which allowed attendees from all over the globe to participate easily.

Thanks to input from our Advisory Board, over the past year the DCRI Think Tanks continued to address critically important topics for clinical research. We discussed the pandemic-fueled shift toward direct-to-patient, virtual, and hybrid trials; wrestled with quality standards for RWD-enabled trials; and debated how to consolidate standards and leverage technology for clinical adjudication. We also tackled the critical issues of systemic racism and bias in clinical research and identified actionable steps to increase inclusion and diversity in clinical trials.

We are deeply grateful for the members of the Think Tank Advisory Board. These industry leaders provide crucial insight and connections that go beyond DCRI’s clinical and operational expertise, enabling the Think Tank program to address the right topics, at the right time, with the right people. We extend our sincerest thanks to our Advisory Board members for their guidance on attendees, framing discussion topics, and contributions to resulting publications.

We look forward to another successful and impactful year.

Regards,

Lesley Curtis, PhD
Chair and Professor
Department of Population Health Sciences
Duke University

Robert Califf, MD
Head of Clinical Policy and Strategy
Verily Life Sciences

“The Think Tanks arose almost spontaneously because of the pressing need for a venue where academics, government scientists and regulators, and the medical products industry could interact to address critical issues that needed resolution. The ability to have a spirited discussion of different points of view—with a goal of finding a path forward—has resulted in tangible progress both in drug and device development and in appropriate implementation.”
“Having attended DCRI Think Tanks since 1995—before the research group was called the DCRI!—I can say that the meetings were, and still are, well-aligned with DCRI’s mission statement. The topics have ranged from the narrow to the very broad, but a hallmark of each was that it addressed a key research, and often policy, question. The discussions and debates have always been very frank, sometimes heated, but always with the notion of moving a field ahead. It was a brilliant maneuver to move the meetings from North Carolina to Washington, D.C. to better facilitate the attendance of key government leaders from NIH, FDA, and other agencies. Aside from the open dialogue in the conference setting, the best part of these meetings was the meal-time and social times where the ‘real’ discussions took place. Congratulations on another DCRI milestone!”

Robert Harrington, MD
Chair, Department of Medicine
Stanford University

<table>
<thead>
<tr>
<th>Think Tank Impact: By the Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
</tr>
<tr>
<td>Meetings</td>
</tr>
<tr>
<td>60+</td>
</tr>
<tr>
<td>Co-Director Collaborators</td>
</tr>
<tr>
<td>146</td>
</tr>
<tr>
<td>Publications</td>
</tr>
<tr>
<td>4,600+</td>
</tr>
<tr>
<td>Attendees</td>
</tr>
</tbody>
</table>
Navigating Clinical Trials in the COVID-19 Era: An Accelerated Shift toward Direct-to-Patient, Virtual, and Hybrid Trials
July 29-30, 2020

CO-DIRECTORS:

Lesley Curtis, PhD
Chair and Professor, Department of Population Health
Duke University

Robert Harrington, MD
Chair and Professor, Department of Medicine
Stanford University

In November 2019, an industry research report highlighted that out of 28 experienced executives across the clinical trials industry, none of them had participated in a fully virtual trial in which there were no physical sites and no face-to-face interactions with patients.

Fast-forward four months to the coronavirus pandemic, and pharma companies, CROs, and sites all rushed to adapt their clinical trials to partial or completely remote monitoring, allowing participants to remain in their homes but continuing to participate in studies. U.S. regulatory authorities demonstrated willingness to allow for appropriate modifications to trial protocols, urging sponsors to document their changes to minimize the impact on the trial integrity.

Additionally, clinicians and patients alike embraced telemedicine like never before to obviate the need for in-person consults.

The coronavirus pandemic catapulted the move toward virtual trials and provided a unique opportunity to reimagine clinical research. This Think Tank meeting specifically addressed how we can translate innovations from this time of crisis into long-lasting, positive changes in the system.

VIRTUAL DISCUSSION FOCUS AREAS:

At the meeting, attendees discussed the below areas; specifically, where we should accelerate full-speed ahead to overcome inertia and where we need to be alert for unintended consequences.

• How can virtual trials be more “person-centered trials” and answer the questions that matter most to patients?
• How can we leverage new methods to answer research questions reliably?
• What areas are ripe for efficient study conduct?
• How can we appropriately approach digital health data?

Key Takeaways:

1. Understanding the regulatory framework for a study intervention remains the biggest challenge to implementing a completely virtual clinical trial.
2. Digital approaches can simplify data acquisitions but have a variety of downstream challenges.
3. A durable, disease-agnostic, public service-oriented infrastructure to support the conduct of clinical trials is needed. Educating and providing information to participants and clinicians is crucial to a trial’s success.
Many are hopeful that real-world data (RWD), including patient-generated data and data derived from routine clinical practice, will provide a credible bridge between the statistically driven world of randomized clinical trials (RCTs) and the traditional, and often anecdotal, practice of medicine. Yet the use of RWD to generate clinical evidence often seems a distant reality. Concerns about RWD quality and uncertainty about expectations for regulatory audits and inspections of RWD-enabled trials pose palpable risks for drug developers, and the benefits remain unclear.

In this workshop we examined a critical question: when and under what conditions should a drug developer decide to include an RWD-enabled trial as a critical element of its therapeutic strategy and regulatory filing? We explored the question by delving into boundary cases where RWD-enabled trials may have presented the only feasible approach for generating clinical evidence. Consider, for example, the use of RWD in rare diseases, to increase size of control arms, or as extended observations for desperately needed therapies that are being used under accelerated regulatory pathways. Alternatively, consider the need for RWD-enabled virtualized trials in the setting of severe Crohn’s disease or other conditions in which bringing the trial to the participant and their data is the only viable option. By exploring these and other examples, we aimed to identify concrete paths forward for RWD-enabled randomized trials in more general cases.

DISCUSSION FOCUS AREAS:

• How are RWD-enabled randomized trials being used to generate evidence in rare diseases? In the setting of virtual trials?

• What have we learned about the quality of RWD across rare diseases and conditions? How does that experience translate to common, chronic conditions?

• What is the experience with quality expectations for regulatory audits and inspections in RWD-enabled trials? What are the considerations regarding the traceability of data?

• When do drug developers consider RWD-enabled randomized trials as a component of pre-market approval and when are such trials a non-starter? What are the considerations?

Key Takeaways:

1. Use of RWD is optimal if the data are fit for the purpose of answering the research question, the endpoint can be ascertained from the data source, the data source includes a sufficient number of patients for sufficient duration, and patient selection in the data source is appropriate. As with evidence from traditional randomized controlled trials, RWE must address pre-specified study objectives, appropriate comparison groups, bias, and trial design elements.

2. Use of remote digital products in clinical trials is growing quickly, and these products are being used to collect patient information to support primary and secondary endpoints. Researchers need to reconcile informed consent with technology terms of service and end user license agreements.

3. Panelists identified the greatest challenges facing RWD-enabled research:

• Getting more patients and providers involved in research to improve the real-world applicability of clinical research findings.

• Understanding that the line between health-related and non-health-related data is becoming less clear, and developing policies for non-discrimination in how those data are used.

• Addressing data quality in EHR systems so that these platforms can be used to capture clinically meaningful outcomes in structured data elements that are easy for clinicians to identify and enter.

Read the executive summary.
Clinical Endpoint Classification and Adjudication – Consolidating Standards and Leveraging Technology
January 27-28, 2021

CO-DIRECTORS:

Renato Lopes, MD, MHS, PhD
Professor of Medicine
Division of Cardiology
Duke University

Kenneth Mahaffey, MD
Professor and Vice Chair of Research
Department of Medicine
Stanford University

The Think Tank session on clinical endpoint classification and adjudication brought together thought leaders from academia, the FDA, and industry to share expert perspectives and best practices around such issues as emerging therapeutic areas and trends in safety and efficacy; CEC independence; ethical use of new technologies, and standards for data quality and compliance. The January 2021 Think Tank session on CEC fostered in-depth exploration and critique of the global insights gleaned from the inaugural CEC Summit, hosted in Chicago in 2018 by Dr. Ken Mahaffey of the Stanford Center for Clinical Research and Dr. Renato Lopes of the Duke Clinical Research Institute.

DISCUSSION FOCUS AREAS:

1. How can the CEC community collaborate on the acceptance and implementation of standardized endpoint definitions in new therapeutic areas?
2. How can artificial intelligence, block chain, and big data be implemented to enhance CEC quality and efficiency, while protecting participant privacy?
3. Consider endpoint ascertainment and methods that provide probabilities of an endpoint based on available data.
4. What are industry and academia perspectives on the impact of COVID-19 and the response by CEC in ongoing trials?
5. Consider utility of mobile and digital methods to ascertain endpoints.
6. What are new approaches or best practices implemented by thought leaders in CEC since 2018?

Key Takeaways:

1. COVID-19 has emerged as a leading cause of death during certain phases of the pandemic, highlighting the need to consider its contributions to specific clinical events and as a competing risk in outcome analyses.
2. The growing use of digital health tools raises questions about validating these tools for data collection. Tech-enabled trials can offer the advantages of speed, efficiency, and scale, but they may need to be organized differently to account for potential complications.
3. Central adjudication offers consistency in endpoint classification, especially in multicenter, multinational trials. There continues to be a need for continued standardization and regulatory guidance.

Read the executive summary.
Inclusion and diversity are urgently needed in all aspects of clinical trials to generate evidence that is generalizable to and trusted by the populations of interest who are most likely to benefit from the practices or products being studied. Fostering an inclusive environment that engages a diversity of participants, sites, staff, and investigators is vital. In this workshop we discussed structures and practices that promote inclusivity and diversity to identify actionable steps that drive meaningful, sustained change in clinical trials and practice.

**DISCUSSION FOCUS AREAS:**

• What are best practices for participant engagement with underrepresented populations during study design, recruitment, and trial execution?

• How can we create mutual benefit and value that drives sustained engagement and retention of underrepresented populations?

• How can the use of digital approaches increase diversity and retention? How can we ensure that we use digital health technologies and tools to eliminate, rather than increase, disparities?

• What are the characteristics and strategies of sites and teams that consistently achieve inclusive enrollment?

• What concrete steps can be taken to develop a more inclusive, diverse network of trial investigators and leaders?

**Key Takeaways:**

1. **Consistent themes in discussions with communities are trust, transparency, and truthfulness.** When engaging communities about clinical research opportunities, researchers and institutions must prove themselves to be trustworthy and be transparent about adverse effects and potential risks or absence of benefits. Research teams should model diversity and inclusion, reflect the diversity of the community, and pay attention to cultural and language issues.

2. Researchers should solicit input from potential participants regarding visit schedules, study design, and materials. Consider how eligibility criteria can disproportionately exclude some groups. Once the protocol is finalized, consider what participant support services are in place and solicit feedback on this ahead of time.

3. **Product design should be approachable and relevant for target populations.** Tools should be accessible to or already in the hands of minority participants. Protocols, consent documents, communications, recruitment and retention plans, and trial experiences should be optimized for diverse participants. Study activities and mechanisms of support should be designed to meet the needs of diverse participants.

Read the executive summary.
The 100th DCRI Think Tank meeting is a major milestone. The DCRI has done a great public health service in organizing these, and I make every effort to attend. The Think Tanks have served as a great opportunity to consider broad issues in the clinical research to care spectrum. They have shaped my view of my own role in this ecosystem, and I am very grateful for the insights I’ve obtained. In the second 100 Think Tanks, I look forward to meetings that serve to launch and engineer new initiatives.”

Norman Stockbridge, MD, PhD
Division Director, Cardiovascular and Renal Products
U.S. Food and Drug Administration, Center for Drug Evaluation and Research

DCRI Think Tanks Advisory Board

Advisory board partnerships with industry leaders help the DCRI Think Tanks program address the right topics, at the right time, with the right people. Our partners provide crucial insight and connections that go beyond DCRI’s clinical and operational expertise. From guidance on attendees, framing discussion topics, and contributions to resulting publications, our advisory board members are players in the lifecycle of every event.

DCRI Think Tanks Leadership

Lesley H. Curtis, PhD
DCRI Think Tanks Faculty Lead
Chair and Professor, Department of Population Health Sciences

Jennifer Gloc
DCRI Think Tanks Program Manager