REGISTRY TRIALS PROJECT
MULTI-STAKEHOLDER EXPERT MEETING

Summary of the Meeting held March 30, 2016

DoubleTree Silver Spring Hotel by Hilton, Silver Spring, MD

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

Meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative (CTTI) website.

Publication Date: June 8, 2016

MEETING BACKGROUND

Demographic, disease, and outcome data collected in clinical observational registries often overlap with data gathered for clinical trials. Integrating clinical trials within observational data registries may offer opportunities to avoid duplicative data collection, increase operational efficiencies, reduce time to database lock and accelerate time to critical decision making, while decreasing clinical trial costs. Questions exist about identifying appropriate registries, ensuring data quality/comparability, meeting regulatory requirements, and processes for implementing a randomized registry trial. The goal of the Registry Trials project is to support the practice of leveraging observational data registries to facilitate high-quality clinical trials. This expert meeting was convened to review the results of the literature review and expert interviews and help develop draft recommendations with input from a diverse group of stakeholders.

MEETING OBJECTIVES

- Identify essential elements of registries needed to successfully embed and conduct registry-based clinical trials
- Present findings from CTTI's Registry Trials Project: Literature Review and Expert Interviews
- Receive feedback on potential benefits of and existing barriers to the use of registries in clinical trials
- Reach consensus on best practices to increase adoption of clinical trials within registries

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MEETING EXECUTIVE SUMMARY

The Registry Trials project convened a meeting involving stakeholders with expertise in this area on March 30, 2016. The participants included more than 43 representatives from academia, government agencies, industry (including pharmaceutical and device companies and contract research organizations), professional service organizations, and patient representatives.

The findings of the literature review and expert interviews were presented, along with experiences from trials conducted within registries. The attendees discussed recommendations for best practices to increase the value, acceptance, and success of registry-based clinical trials. Suggestions were generated around four topic areas: data quality, regulatory issues, governance, and registry design.

Themes that emerged throughout the meeting included:

1. There is a role for registries in creating a sustainable infrastructure to conduct regulatory trials, including early development, pre-market, and post-approval investigations;

2. There is a continuum of registry type/characteristics (e.g., location, purpose, and design, etc.) across the ecosystem that makes some registries more appropriate for conducting registry trials; and

3. Designing or altering registries so that they are fit for purpose for a Randomized Registry Clinical Trial (RRCT) necessarily involves a myriad of considerations, including, but not limited to, informed consent, governance, interoperability, connectivity, flexibility, sustainability, data quality, regulatory, privacy, and the business model.

The Registry Trials project team will consider the evidence gathered and input from the meeting in developing project recommendations, which will be finalized and disseminated via formal CTTI procedures.

MEETING SUMMARY

The meeting began with presentations that summarized CTTI methodology and the objectives of the Registry Trials project. The Registry Trials project focuses on how to use clinical registries in the context of prospective registry-embedded clinical trials to support traditional pre-and post-marketing studies. The use of other large data sets (e.g., electronic health records [EHRs], comparative effectiveness research) are outside the scope of the project.

It was noted that the project uses an adapted version of the European Medicines Agency definition of registry:

> *"An organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry)."*

Regulatory Pathways: Devices vs. Drugs—Are There Roles for Registries?

John Laschinger, MD, of the Food and Drug Administration, compared and contrasted the potential for pre-market use of registry data for drug and device evaluation. For

drugs, uncontrolled or partially controlled studies are not usually acceptable as the sole basis for approval of claims of effectiveness (even for label expansions). However, for devices, the evidence requirements vary, and partially controlled studies or reports of human experience may be acceptable, if determined to provide reasonable assurance of safety and effectiveness, and provide the evidence necessary to assess and assure a favorable benefit-risk balance. Dr. Laschinger explained that for new devices, controlled trials are generally required, but for label expansions or iterations on an already approved device, use of existing data from real-world use may be an acceptable source for evidence needed for a regulatory decision. When considering the use of either retrospective or prospective registry data as a source for evidence, two key considerations are data quality and fitness for purpose. The data must be reliable, robust, and relevant to the question at hand. Overall, it was felt that there is a role for registries in creating a sustainable infrastructure to conduct prospective clinical trials, including pre and post market trials needed to produce the evidence required for regulatory decisions, as well as the infrastructure needed for vigilant post-market surveillance. However, it will require upfront planning to ensure the data are high quality and fit to purpose for generation of evidence needed to inform clinical and regulatory decisions. In addition to "quality by design," additional considerations critical to the successful use of registries include interoperability, connectivity, flexibility, responsibilities for monitoring, developing the incentives and utility to encourage routine use (i.e., sustainability), as well as patient identification, randomization and protection.

During the discussion that followed, it was mentioned that registries provide access to additional clinical data collected before a trial that would not normally be available in a traditional trial. Another advantage is the inclusion of patient-reported outcomes.

One challenge was whether a drug or device provided to patients at no cost during a trial would require payment from patients to continue receiving it after the trial ended. This issue is not specific to registry-embedded trials and is being addressed with insurance companies (payers) and the Centers for Medicare & Medicaid Services (CMS). It was recognized that registries designed to capture individual episodes of care or intervention may be better suited for shorter-term outcomes, and that linkages with other databases (e.g., other episodic care registries, CMS administrative data, Social Security Administration Master Death File, etc.) may be available sources for longer-term outcomes. The most effective registries should not require clinicians to make changes to their workflow and will have additional purposes (e.g. use for quality assessment, performance improvement, risk prediction, benchmarking) that promote sustainability beyond a single trial. Attendees expressed that the definition of a "registry" may vary, and there may be some overlap with what some consider to be a prospective cohort. However, for the purposes of this project, a "registry" is an organized system using observational methods that could allow multiple studies to be embedded within it. A primary data collection cohort study conducted solely to meet specific study objectives does not meet the project's definition. Ultimately, a study-specific cohort could eventually become a registry as defined for this project.

Presentation of Project Findings

Team members presented an overview of the project's literature review and expert interview results.

Literature Review

As part of the evidence gathering for this project, two literature searches were conducted: a broad search investigating the relationship between trials and registries, followed by a more targeted search focusing on the role of registries in post-approval studies. Publications since 2005 were included if they described the use of a clinical registry in any stage of the clinical trial process (e.g., planning, recruitment, long-term follow-up), were commentaries/editorials about randomized registry trials, were examples of registry-based clinical trials, or were examples of studies that could inform the future conduct of a registry-based clinical trial. Nearly 300 articles were included in the qualitative synthesis, while the presentation focused on a subset of 30 publications. The subset focused on randomized registry clinical trials and commentaries about embedding trials within registries. According to the publications, common uses of registries to facilitate clinical trials were in design (e.g., develop research questions, refine eligibility criteria), conduct (e.g., trial site selection, recruitment, data collection, support follow-up), and post-trial validation and surveillance (e.g., post-approval studies, safety surveillance, evaluating off-label use). Advantages and disadvantages of using data from registries versus data gathered in randomized controlled trials (RCTs), according to the publications, are show in Figure 1.

Figure 1. Advantages and Disadvantages of Registries vs. RCTs

	Advantages	Disadvantages

Registry	• Continuous
	• Descriptions of landscape, standards, treatment patterns
	• Large, heterogeneous populations (generalizable)
	• Detect rare events
	• Inexpensive
		• Limited value for inferring causal relationships
		  • Potential confounding
		  • Missing data, data quality variable/questioned
		• Utility varies based on type of registry
		• Limited interoperability

Randomized Clinical Trial	• Randomization balances variation and confounding factors • Detect small-to-moderate effects reliably with adequate sample sizes • Good data quality	• Strict eligibility criteria • Expensive • Logistically complex • Discontinuous • Patient burden • Site/Provider burden • Misaligned industry incentives and patient need

James and colleagues (Nat Rev Cardiol 2015) published a definition of a registry-based RCT (RRCT): a prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting. Examples of RRCTs included the following: SORT OUT II-VII (Denmark), TASTE (Sweden, Denmark, Iceland), iFR-SWEDEHEART (Sweden, Denmark), PROTECT-TAVI (Italy), REPLACE (Italy), and SAFE-PCI for Women (US). Many of these trials take advantage of national health registries combined with disease-specific registries. In some cases, investigators were able to conduct several trials using the same registry infrastructure. The transcatheter valve therapy (TVT) registry is an example of registry combining data from multiple sources through partnerships among the FDA, CMS, academic societies, and the Duke Clinical Research Institute (DCRI). CORRONA is an example of adding additional modular datasets to a registry for the purposes of a clinical trial, then relying on the registry for long-term follow-up.

Overall, the literature revealed that the type and purpose of the registry is important to determine if embedding a clinical trial is possible and appropriate. Considerations include data completeness, data quality, interoperability, representativeness, informed consent, and privacy. There are also cost/operational questions such as who will fund the registry, which party will pay for adjustments required for clinical trials, and who will be responsible for maintenance costs.

Expert Interviews

Structured interviews were conducted with 25 experts to gather opinions regarding the feasibility of using clinical registries for prospective clinical trials. There was broad agreement among the experts on the proposed definition of registry (adapted from the EMA definition), though it was noted that this definition differs from the Agency for Healthcare Research and Quality definition. There was also agreement that registries can be more widely used to facilitate embedded clinical trials. Some experts expressed that registries are primarily valuable for recruitment. Concerns included bias and variability. Most experts also felt that some adaption of registry items would work for clinical trials, though some comments indicated that registries should be set up from the beginning to support trials.

Data quality was consistently identified as a potential weakness of registries. In contrast, no clear consensus emerged with regard to potential strengths of registries. Multiple strengths were noted across several broad categories, such as efficiency/cost efficiency, recruitment, study design, large datasets, and a more real-life population. In terms of most pressing issues for registries, there was no clear leading issue that should be tackled first. Among the most frequently cited were a lack of will among leaders, data harmonization and standardization, reliability of data, and regulatory flexibility. Overall, there were a variety of suggestions for short-term actionable items, and further discussion is needed around the best way to address them (e.g., publications, consensus building, infrastructure). For long-term actionable items, the development of registries, costs, and data issues were suggested. Questions included whether registries should be voluntary or mandated and domestic or international, what are the elements of a sustainable and scalable business model, and how the data issues relate to other initiatives (e.g., EHRs).

Discussion

In the discussion that followed, it was suggested that stronger calls to action may be needed beyond the suggestions of best practices from CTTI in order to accomplish the goal of increasing adoption of clinical trials within registries. The TAVR registry has used the approach of CMS requiring data input for reimbursement, but there have been challenges with the complexity of data entry required. Attendees stressed that the importance of simplifying data collection to minimize the burden on clinicians and cost. Though data collection can be expanded when needed for a particular embedded clinical trial, others noted that a balance must be struck, because modifying a registry for each clinical trial may be impractical. It was suggested to clarify with the FDA which data are actually needed in order to avoid collecting unnecessary endpoints. To get leadership buy-in, showing registries' value to hospitals for performance improvement, benchmarking, etc. was expected to help.

There were questions regarding whether data from an embedded clinical trial could remain within the registry to enrich the resource. Sponsor and privacy concerns would need to be considered, but there have been some models for this. For example, advanced cancer registries anonymize the investigative agent to avoid collecting data on another sponsor's drug.

A suggestion for an international collaboration was brought forward. Such a registry study could serve as a proof of concept for multi-sponsor involvement and allow recommendations to be developed for overcoming barriers. It would need to be in a carefully selected therapeutic area and involve a limited set of data elements. Others noted that differences in regulatory guidelines and challenges combining data across countries may complicate such an effort. It was mentioned that the American Congress of Obstetricians and Gynecologists is starting an international project called Devices Without Borders.

The tracking of long-term outcomes in registries was an area felt not to have been addressed in the findings presented. For example, without a unique medical identifier in the United States, how to track outcomes for individual patients over time when they change doctors and health systems. Attendees were also surprised that experts had not been asked about the long-term sustainability and business model for registries.

Case Studies

Three investigators from around the world with experience conducting trials in registries were invited to present their experiences to generate discussion and inform best practices.

TASTE Trial

Ole Frøbert, MD, PhD, presented lessons from the TASTE trial, which was an RCT embedded in the SWEDEHEART registry, a national cardiac registry in Sweden with 80,000 cases annually. The trial tested thrombus aspiration, a simple technique with little evidence, for patients with ST-elevation myocardial infarction. About 50% of percutaneous intervention procedures in Sweden were already using this procedure. The primary endpoint was all-cause death at 30 days. A physician or nurse completed

the data entry for the registry, and there were linkages with a population registry for other data questions. Only two questions were added for the trial in the registry form, one about informed consent and one about exclusion criteria.

The trial enrolled >60% of all patients with the diagnosis and >75% of those eligible to participate. No patients were lost to follow-up and no differences were observed between the two groups for the primary and secondary endpoints. A subsequent larger, traditional RCT conducted in Canada reached the same conclusion. While it was estimated that the TASTE trial would have cost $14M if done as a traditional RCT, the actual total cost was $300,000 or approximately $50 per patient (all costs USD). This represents just 2% of the costs of a traditional clinical trial.

Dr. Frøbert stated that RRCTs can be used for marketed devices and treatment strategies, while traditional RCTs should be used for new drugs and first-in-human devices. The RRCT is best suited for a single clinical hypothesis that has broad inclusion criteria and hard endpoints. One lesson from the TASTE trial included the importance of keeping registry-embedded trials simple. There was a simple randomization schema, no outcome adjudication, and there was limited additional workload and reduced monitoring. In addition, the study design team realized the need for collaboration, including having patient representatives involved from the beginning and enrolling all treatment centers, not just university hospitals. The small centers enjoyed participating in TASTE and many had the best inclusion rates despite having not participated in a randomized trial in an acute setting before. Having inclusion rates available online allowed sites to see their rates versus other sites and motivated performance. The TASTE investigators faced a challenge with informed consent. They originally planned to include comatose patients as well but this was denied by the central ethical committee in Sweden. The TASTE trial highlights the power and potential efficiencies of the RRCT concept. Dr. Frøbert concluded by explaining that the key consideration to conducting registry embedded trials is keeping things "simple, simple, simple".

Industry-Sponsored Oncology Registries for Clinical Trials

Dawn Flick, RPh, MPH, ScD, presented examples of industry-sponsored oncology registries, which were prospective observational cohort studies for treatments for advanced solid tumors. These were not post-marketing commitments, and they were primarily in community settings (>200 sites nationwide).

The studies had broad objectives and are often hypothesis-generating. An external scientific steering committee (SSC), which may be composed of key opinion leaders, study investigators, statisticians, and patient advocates, reviewed the study protocol and provided guidance on study design, conduct and publications. In the registry, sites transferred data from the patient's medical chart into a separate electronic data capture system. The patients were followed and treated per standard of care, solely at the clinician's discretion. A challenge in oncology registries is allowing enough time for the site to enroll patients after the cancer diagnosis or start of treatment date without introducing a survivorship/selection bias into the sampled patient population. To reduce information bias (from missing or erroneous data), data should be cleaned regularly via site queries throughout the course of the study, but there is minimal source data

verification or monitoring. In collaboration with the SSC, analyses were conducted biannually for publication purposes. These are multimillion dollar, resource intensive studies.

Dr. Flick explained that the most important considerations for registry study design, in order to make them fit for the purpose of embedding clinical trials, are to diminish causes for delays in enrollment into the registry, make the necessary efforts to keep patients on study (reduce loss to follow-up), and to find the right balance in data cleaning that maintains data integrity without overburdening the sites. Additional considerations include that sites and staff may not be trained for conducting clinical trials, additional IRB approval is needed for each trial, and active patients would need to be re-consented for each trial. In addition, follow-up visits, types of procedures, diagnostic tests, and response criteria would need to be protocol-specified and mandated once the patient enrolls in the trial. Trials also require comprehensive safety collection and have expedited reporting requirements. Budget adjustments may be necessary, because site fees for data entry are generally lower for a registry than for a clinical trial. She noted that registry data can become outdated quickly, and more modifiable protocols and company standard operating procedures/guidance documents are needed since oftentimes in industry these were set up for traditional RCTs and not registries. More external collaborations and multiple partnerships are also needed.

Veterans Affairs Point of Care Clinical Trial and Precision Oncology Programs

Louis Fiore, MD, MPH, shared experiences from embedded trials in healthcare systems at Veterans Affairs (VA). The VA has 10 million subscribers, and their corporate data warehouse is like a big registry. He described three examples of clinical trials within their system. In the first, patients were randomized at the point of care to either a sliding scale or weight-based insulin regimens when their doctor agreed. This was done through the EHR, and a nurse obtained informed consent. In the second example, they used the corporate data warehouse to identify patients who would be eligible for a trial comparing different diuretics, then contacted the provider about switching the patient's drug. There was no additional staff or case report forms for the trial, and everything was implemented through the EHR. Finally, the Precision Oncology Program is registry based and captures data on tumor sequencing, imaging, and clinical data from regular care. The VA is just starting to do clinical trials through this program.

Lessons from the VA's experience include only making the data as good as you need it to be. To assure data quality, they conduct cleanup as needed depending on the data use. Dr. Fiore explained that the culture of conducting trials in health systems is different—questions must be relevant to the health systems, clinicians, and patients. These stakeholders do not appreciate "bedside to bookshelf." Some clinicians were hesitant to participate because they had strong treatment preferences, but overall, when there was an effort to engage providers at start-up, participation was strong. Initial concerns from providers included lack of autonomy and additional burden of the research, but with an educational rollout, they were able to alleviate these concerns and show the value of the research to the health system. In talking to patients, patients were a lot less concerned about data privacy than they expected. The majority wanted their data to be used to help make healthcare better. Challenges included regulatory questions such as whether clinicians had to complete research training if they were only

doing standard procedures. There was some missing data, and the largely unstructured data makes electronic phenotyping difficult. However, the VA setting made some things easier since it is a single payer with long follow-up and a single EHR.

Discussion

In the discussion that followed, attendees questioned the business model for some of these programs and trials. The SWEDEHEART registry is funded through national sources, and outside contributions are obtained as needed for trials. The VA is using funds from its healthcare system rather than research office to conduct the research described, and is working to break down silos between research and healthcare. There was a recommendation for CTTI to consider partnering with the Patient-Centered Outcomes Research Institute and some large health systems to target some of the stakeholders perceived to have a lack of will.

Best Practices

In the final activity of the meeting, attendees divided into breakout sessions addressing four topic areas to discuss recommendations for best practices to increase the value, acceptance, and success of registry-based clinical trials. The suggested best practices were then presented to the larger group for additional discussion.

Data Quality

The group addressing data quality began with a simple definition of data quality as "the absence of errors that matter." This definition encompasses the completeness of data as well as fitness for purpose, and it reflects the reality of clinical data. A question that should be asked when considering data quality is, "what is the information upon which decisions are made?" A suggested reference document is the NIH Health Care Systems Research Collaboratory's recommendations for data quality assessment for pragmatic clinical trials.

With regard to whether the standards for registry-based trials' data quality should be the same as pre-market trials, the group felt that more guidance from the FDA was needed. A suggestion was to start having conversations around specific data quality assessment plans. A suggested best practice was to ensure protocols and procedures include such plans. There are ways that registries could be changed to meet higher standards in terms of both software and data. Questions include whether software would need to meet FDA clinical trial requirements (e.g., CFR-21 Part 11 compliance, CDRH guidance on software validation). It was suggested that there be a customized approach/risk assessment for data quality. Adjudication should be driven by risks to the patients and study integrity. However, there is also a risk that lower-quality data reported to the FDA could delay approvals.

Attendees noted that it would be beneficial to try and determine the rules early for this new concept. Consumers of the research would like some assurances of the quality. It was also mentioned that there may be other dimensions to data quality, such as whether the data are answering the questions of relevance to patients; an example given was the need for long-term outcomes for ADHD medications.

In summary, the group's recommendations were as follows:

- Clearly define data quality
- Risk assessment based on what is needed and not needed
- Depends on the question to be answered or the purpose of the registry
- Data quality section in the statistical analysis plan (and potentially data management plans) should discuss the degree and/or randomness of missing data, as well as sensitivity analyses
- Data quality is the responsibility of the registry study designers and analysts (statisticians), but guidance is also needed from stakeholders including regulators, reviewers (journals), and payers

Registry Design

Regarding best practices/solutions for registry design, there was consensus that disease-specific registries are more sustainable and valuable than therapy-specific registries. The group noted that to have sustainable registries, they should not be designed for a single, narrow purpose; in other words, there needs to be a business model framework. The group thought about how to make optimal use of the registries that exist today as well as to design for the future. Overall, it was felt that increased collaboration among healthcare systems, industry, payers, academics, and regulators is needed. Trialists and registry owners should think about how to collaborate, and there should be transparent discussions with regulators about how a registry will be used. The group recommended to stop doing pilots and move forward with doing registries to help develop the business model. International collaborative registry studies in a certain disease areas were mentioned as a way forward.

Additional suggestions included the following:

- Make it easier to look for existing data sources, such as by encouraging participation in AHRQ's registry of registries
- Partner with stakeholders from the start—not just doctors, but end users, patients, etc.
- Stakeholders have different motivations for developing registries; develop collaborations and gather multi-stakeholder input to influence registry design
- Keep registry design simple and add on as needed
- Have the capacity to add adjudication but only when needed based on the research question
- Need greater data standards
- Need an overall culture change to incorporate learning into healthcare systems
- Rethink how to do clinical trials through registries. Don't try to apply the old ways of thinking

Regulatory

Regarding informed consent for registry trials, there is currently a challenge in that the Common Rule allows for waiver of informed consent, but FDA part 50 regulations do not. Although there is hope for these regulations to be harmonized (work is in progress),

the group noted that currently, if the data is intended to be submitted to regulators, there needs to be informed consent.

In terms of data quality, data for regulatory submissions needs to be reliable, robust, and relevant. It should also be audited for internal or external validity using a risk-based model. In general, the group stated that if the standards for well-conducted RCTs are being followed, then the data should be acceptable for regulatory submissions. Data audits could employ some of the same principles as for RCTs; for example, automatic queries for out-of-range values. External validity could be assessed through site audits for a percentage selected sites participating in a registry based on certain criteria.

In summary, the suggested best practices were as follows:

- Pre-planning is better than retrofitting
- If a new registry is being created with intent to submit data for regulatory purposes:
    - Set up a registry process to obtain informed consent and permission to contact patients
    - Set up the registry as Part 11 compliant (electronic standards)
- Ability to incorporate modular add-ons to existing registries
- Combine registry workflow with study workflow
- Ability to link to other data registries

Attendees raised some concerns that the recommendations for monitoring and Part 11 compliance not be made too stringent. Though being Part 11 compliant would help facilitate some clinical trials, this may be too high a burden for many smaller registries. Data monitoring can also balloon costs. During the design phase, it was suggested to consider the likelihood for whether a registry will be used to provide data for regulatory submissions, which could inform the level of resource investment.

Though registry data have been used to support regulatory decisions for devices, it was stated that regulators are not yet convinced that historically or externally controlled trials using registries could support regulatory decisions for drugs. A major issue is the effect sizes in drug trials typically are not large enough to support new indications. Adoption of data from registries for drug decisions will likely require additional data comparing registry data to traditional randomized controlled trials or collecting additional data outside of the registry. However, regulators believe registries can be useful now for identifying patients for trials and learning about natural history. Speaking with the FDA about what evidence would be required was also suggested.

Attendees reiterated that the focus of this project is on best practices to increase adoption of embedding randomized clinical trials within registries. Issues of quality related to using existing registry data as external or historical controls for regulatory purposes is informative to, but outside the focus of, the Registry Trials Project.

Governance

The recommended best practices/solutions around registry governance were as follows:

- Establishing the registry intent
- Have a detailed process and structure
- Develop a decision tree to decide if informed consent is needed

There was no consensus on whether to establish a governing body for a registry first or after the registry intent is outlined. Though the makeup of governing bodies vary, there was agreement that multiple stakeholders should be involved in governance, including those who will use the data. Detailed processes and structures are needed to outline who owns the data and how the data will be shared. There are increasing pressures for access to individual patient data, making the oversight structure very important. It should also be recognized that the governing body and processes may need to change over time. When developing a decision tree for informed consent, national, state, and local laws will need to be considered. Most of the group agreed to err on the side of obtaining prospective informed consent for all registries, but some maintained that it depends on the purpose of the registry. However, it may also be hard to predict all the potential future uses of registry data. There can be gray areas around quality improvement studies and retrospective reviews. The NIH Health Care Systems Research Collaboratory has explored informed consent issues for pragmatic clinical trials, so those materials may be relevant.

Conclusion and Next Steps

From the day's discussion, a framework had begun to construct the project's recommendations. The project team will use the thoughts and ideas that were gathered to generate recommendations and useful tools to disseminate to the clinical research community.

FUNDING STATEMENT

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ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and drive adoption of practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

For more information, contact the Registry Trials Project Manager Steve Mikita at steve.mikita@duke.edu or visit http://www.ctti-clinicaltrials.org.

Appendix A. Meeting Agenda

REGISTRY TRIALS PROJECT

A Brave New World: Registry-Based Clinical Trials

Agenda of the Multi-Stakeholder Expert Meeting held March 30, 2016

DoubleTree Silver Spring Hotel by Hilton

8727 Colesville Road

Silver Spring, MD 20910

CTTI MISSION: To identify and promote practices that will increase the quality and efficiency of clinical trials

MEETING OBJECTIVES:

- **Identify essential elements of registries needed to successfully embed and conduct registry-based clinical trials**
- **Present findings from CTTI's Registry Trials Project: Literature Review and Expert Interviews**
- **Receive feedback on potential benefits of and existing barriers to the use of registries in clinical trials**
- **Reach consensus on best practices to increase adoption of clinical trials within registries**

March 30, 2016

8:00 **Breakfast** *(Provided)*

8:30 **Welcoming Remarks**

8:30 Welcome, Meeting Agenda
Stephen Mikita, Registry Trials Project Manager

8:35 Introduction to the Clinical Trials Transformation Initiative
Sara Calvert, Clinical Trials Transformation Initiative

8:50 9:30 **Session I: The Registry Trials Project Scope, Overview, and Regulatory Pathways**

Session I Facilitator: John Laschinger; Food and Drug Administration
Session I Objectives:
- *Describe project background, overview, and scope*
- *Review U.S. regulatory pathways*

8:50 Registry Trials Project Overview and Scope
Stephen Mikita

9:00 Regulatory Pathways: Devices vs. Drugs - Are There Roles for Registries?
John Laschinger, FDA

9:15 Open Discussion

9:30 10:45 **Session II: Presentation of Project Findings**

Session II Facilitator: James Tcheng, Duke University
Session II Objectives:
- *Present findings from literature review*
- *Present findings from expert interviews*
- *Discuss findings, barriers and solutions*

9:30 Registry Trials Project Literature Review
Sara Calvert, CTTI

9:45 **Break** *(Refreshments Provided)*

10:00 Registry Trials Project Expert Interviews
Ted Lystig, Medtronic

10:20 Open Discussion

10:45 12:15 **Session III: Expert Panel, Registry Trials Lessons Learned**

Session III Facilitator: John Laschinger, FDA
Session Objectives:
- *Provide examples of previous experience with registry trials*
- *Identify major challenges/barriers to registry trial implementation*
- *Discuss generalizability and actionable solutions*

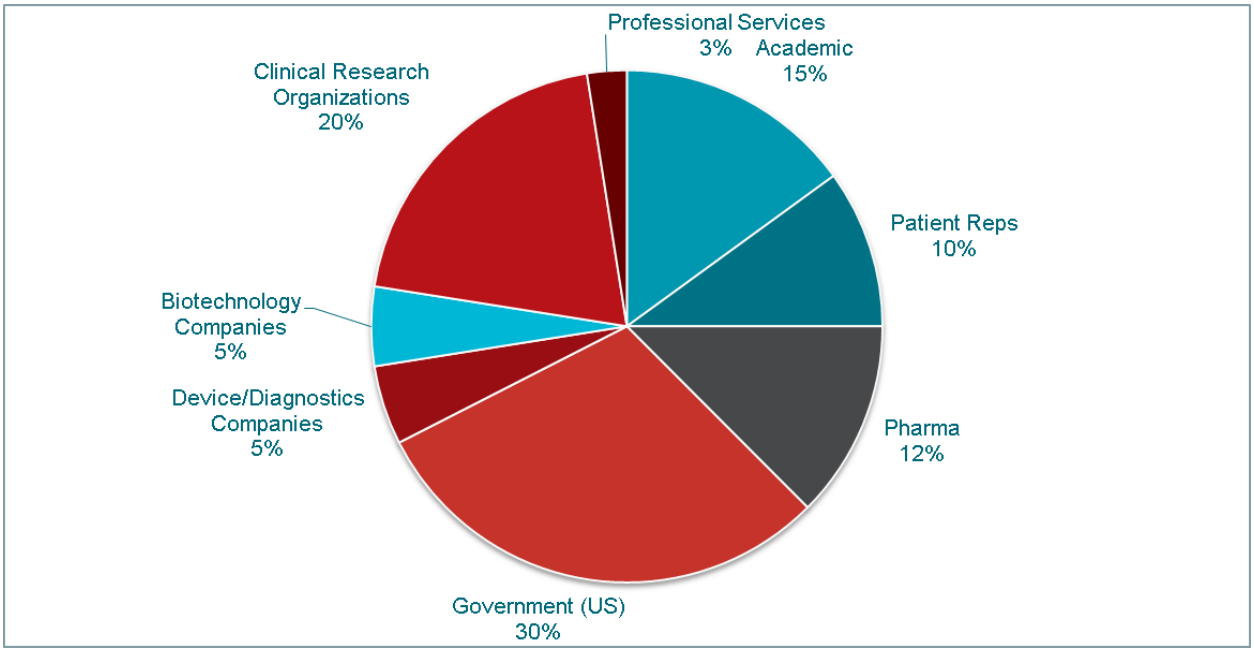
March 30, 2016

10:45 12:15	**Session III** *(Continued)*
10:45	Registry-based RCTs: Lessons from the TASTE Trial *Ole Frøbert, Örebro University Hospital*
11:05	Utility of Industry-Sponsored Oncology Registries for Clinical Trials *Dawn Flick, Celgene Corporation*
11:20	The VA's Point of Care Clinical Trial and Precision Oncology Programs *Louis Fiore, Department of Veterans Affairs*
11:35	Open Discussion
12:15	**Working Lunch** *(Provided)* *Introduction to Breakout Sessions and Group Assignments*
1:15 2:15	**Session IV: Breakout Sessions, Best Practices**
	Session IV Facilitator: Ted Lystig, Medtronic *Session IV Objective: Propose best practices to increase adoption of registry-based clinical trials* **Breakout 1: Data Quality** *Facilitator: Jules Mitchel, Target Health* **Breakout 2: Registry Design** *Facilitator: Nicolle Gatto, Pfizer* **Breakout 3: Regulatory** *Facilitator: Kristen Miller, Food and Drug Administration* **Breakout 4: Governance** *Facilitator: Arlene Swern, Celgene Corporation*
2:15	**Break** *(Refreshments Provided)*
2:30 4:00	**Session V: Breakout Sessions Report Outs, Best Practices**
2:30	Breakout 1: Data Quality *(Presenter TBD)*
2:45	Breakout 2: Registry Design *(Presenter TBD)*
3:00	Breakout 3: Regulatory *(Presenter TBD)*
3:15	Breakout 4: Governance *(Presenter TBD)*
3:30	Open Discussion/Consensus Recommendations
4:00 4:15	**Session VI: Call to Action and Wrap up**
	Session VI Facilitators: James Tcheng, John Laschinger, and Ted Lystig
4:15	Adjourn and Departures

Appendix B. Meeting Participants

Our meeting participants included representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties. Participants actively engaged in dialogue throughout the day.

STAKEHOLDERS REPRESENTED



MEETING ATTENDEES

Ron Bartek	Friedreich's Ataxia Research Alliance (FARA)
Elise Berliner	AHRQ
Mary Brophy	VA Boston Healthcare System
Chunrong Cheng	Food and Drug Administration, CBER
Christopher Dowd	Cystic Fibrosis Foundation
Ryan Ferguson	Department of Veterans Affairs
Louis Fiore	Department of Veterans Affairs
Dawn Flick	Celgene Corporation
Ole Fröbert	Örebro University Hospital
Nicolle Gatto	Pzifer
Eric Gemmen	Quintiles, Inc.
Cale Jacobs	University of Kentucky
Jeffrey Joseph	Chiltern International
John Laschinger	Food and Drug Administration, CDRH
Christian Lattermann	University of Kentucky
Beverly Lorell	King & Spalding

MEETING ATTENDEES (Continued)

Theodore Lystig	Medtronic
Olga Marchenko	Quintiles, Inc.
Kimberly McCleary	Faster Cures
Lauren McLaughin	Michael J Fox Foundation
Eva Miller	Inventiv Health
Kristen Miller	Food and Drug Administration, CDER
Jules Mitchel	Target Health Inc.
Christopher Mullin	NAMSA
Bob O'Neill	Food and Drug Administration, CDER
Angelo Ponirakis	American College of Cardiology (ACC)
Thomas Rhodes	Merck & Co. Inc.
Rachael Richesson	Duke, AMIA
Sukhie Sandhu	Food and Drug Administration, CDER
Jeffrey Sherman	DIA
David Shih	Food and Drug Administration, CDER
Mats Sundgren	AstraZeneca
Arlene Swern	Celgene Corporation
James Tcheng	Duke University Medical Center
Robert Temple	Food and Drug Administration, CDER
Fran Thorpe	American College of Cardiology (ACC)
Karen Ulisney	Food and Drug Administration, CDRH
Angela Walker	Eli Lilly and Company
Emily Zeitler	Duke University Medical Center

STAFF

Sara Calvert	Clinical Trials Transformation Initiative
Stephen Mikita	Registry Trials Project Manager
Kimberley Smith	Clinical Trials Transformation Initiative
Gina Uhlenbrauck	Duke Clinical Research Institute