Registry Trials Project
Expert Interviews

Prepared for:
Clinical Trials Transformation Initiative (CTTI)

Prepared by:
RTI International

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Contents

1 Background

Data collected in registries can overlap with data needed for a clinical trial. As such, CTTI has been tasked with looking into the use of registry data to facilitate clinical research. The ultimate success for using registry data is pulling all the data needed to answer a research question from within a registry database. There are examples where researchers were able to answer important research questions from existing registry databases. Post-marketing registries have been useful for gathering the evidence needed to expand the use and/or applicable populations for an approved drug or device. By researching this potential avenue for streamlining research efforts, the goals of this project are to identify ways to become more efficient, avoid collecting the same data more than once, and decrease the resources (time and money) to do research.

If using registries for clinical trials is to be adopted as a methodologically sound research possibility, then important questions about registry data quality, regulatory requirements, privacy, and optimal registry infrastructure must be answered.

This particular portion of the CTTI Registry Trials Project focuses on gathering expert opinions, including barriers and potential solutions, regarding the feasibility of using clinical registries for prospective clinical trials. Although large databases, like electronic health records (EHRs), were determined to be beyond the scope of the CTTI Registry Trials Project, it is worth noting that when discussing interoperability (comprising overlapping focuses: use of common data elements, pulling data from multiple sources, and ability to follow a subject across multiple databases), the topic of EHRs came up frequently.

2 Methods

2.1 Interviewee Selection and Recruitment

CTTI invited experts who have knowledge regarding the use of registry data in clinical trials to be interviewed. The interviewees (listed in Appendix A: Table of Interviewees) spanned a variety of perspectives. These individuals included representatives from existing registries, pharmaceutical companies, federal agencies, and academic institutions. The interviewees' backgrounds and expertise spanned everything from physicians, statisticians, epidemiologists, and lawyers, to private citizens who are championing disease registries. Of the thirty-seven individuals that CTTI staff invited (via email solicitations), twenty-nine agreed to be interviewed. RTI staff consulted with CTTI in order to prioritize which twenty-five interviews to proceed with, per the contracted scope of work, in order to assure the most comprehensive variety of perspectives. RTI staff followed up with the resulting list of interviewees to schedule the interviews.

2.2 Interview Guide

RTI staff conducted twenty-five interviews, based on a structured interview guide that ensured all participants would be asked the same series of questions. RTI collaborated with CTTI to

review and refine the structured interview guide, which included many open-ended questions. An RTI survey methodologist reviewed the interview guide and discussed interview execution with RTI staff who were conducting the interviews. Discussion points included how to probe for more detailed information and listen actively by echoing key points back to participants.

The guide was pilot tested in the first three interviews. The write-up of the responses were sent to the CTTI team for review and comment on October 28, 2015. After reviewing, no changes to the Interview Guide were requested for the balance of the interviews.

The guide's questions covered the following interview sections:

- Confirming Registry Definition
- Feasibility of Using Registries for Embedded Clinical Trials
- Strengths and Weaknesses of Registries
- Barriers and Potential Solutions (divided into 2 tiers of priority)
- Device Registries and Trials: Experience, Differences between Drug and Device Trials
- Adapting Registry (Tools, Experience, Regulations) for Drug or Device Trials
- Operational Adjustments for Registries to be Used in Clinical Trials
- Prioritized Issues
- Actionable Items: Near-term and Long-term

2.3 Interviews

The interviews were scheduled and completed between October 13, 2015 and November 23, 2015. All twenty-five interviewees gave their verbal consent to be interviewed, to be listed as an interviewee within this report, and to have their interviews digitally recorded to ensure that the interview data was accurately captured and transcribed. In some instances, the interviewer reframed or rephrased questions based on a participant's response or skipped questions that a participant had already addressed or indicated were not relevant. The structured interview guide also included probe questions to gain more detail when applicable.

Interviewees were told that interviews, on average, would last an hour. In reality they spanned from twenty-five to ninety minutes. Each interview teleconference call included the expert being interviewed, an RTI interviewer, and an RTI staff member to transcribe the interview. As mentioned above, all interviews were digitally recorded to assure the complete transcription of responses. As a second step for data quality, the RTI project manager did a review of each transcription for accuracy and completeness. Edits were done as needed, utilizing the digital recordings for source data verification.

2.4 Coding

RTI staff copied the interview responses into a spreadsheet for coding. The responses were then coded in order to summarize responses and identify any recurrent themes for each question. The coding process was iterative, with both adding of codes for new ideas and combining responses that captured the same concept as more interviews were conducted.

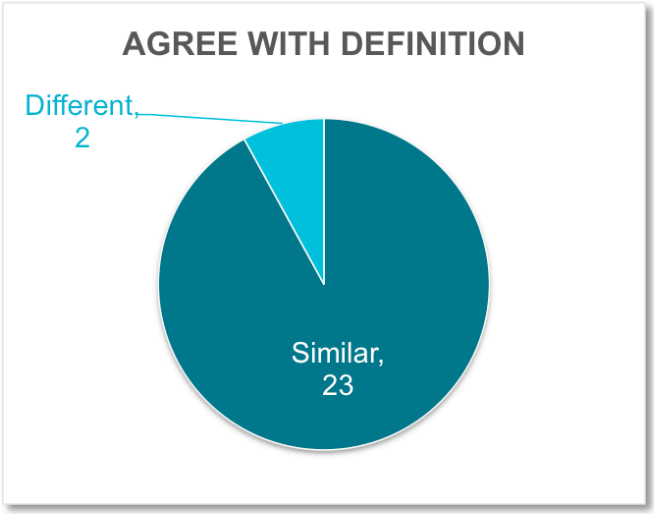
Once ten sets of interview responses were transcribed, the data (along with preliminary coding of the data), were shared with the CTTI team. There were no specific recommendations for coding of the data based on this meeting with the CTTI team, and the RTI team proceeded with the transcription and reviews of the data, as well as coding the interview question responses.

Interview data, including graphs of response frequency and identified themes, are captured and detailed in the following sections of this report.

3 Interview Responses

3.1 Agreement with Definition of Registry

An adapted version of the EMA's definition of registry is being used for this project: "*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).*" [Source: EMA: Guideline on good pharmacovigilance practices (GVP).] The majority of the interviewees agreed with this definition.



3.1.1 Disagreement with Definition

There were two interviewees who stated that they had a different definition of a registry, summarized below:

1. *What is different about this definition and the AHRQ definition is that the AHRQ definition also states, "serve one or more predetermined scientific, clinical, or policy purposes." That part is different from the definition that was read, and is a very essential piece that should be included in the definition defining what a patient registry is, because it is the key purpose of patient registries.*
2. *The term registry has do with demographic information primarily, a little bit of diagnostic information, but this is primarily a tool for communication and recruitment for research. For instance, contact registries help to determine the registrants that are diagnosed with the disease the registry collects data for, and to determine which of the patients enrolled in the registry might be eligible for any particular research project, usually a clinical trial.*

3.1.2 Additional Thoughts on Definition

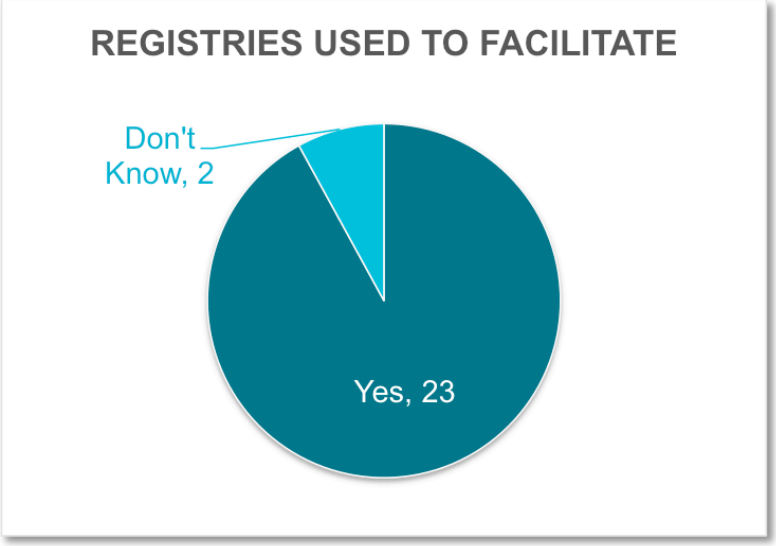
There were other comments from interviewees who thought the EMA's definition of a registry was similar to their thoughts, but they had some additional thoughts on the subject.

1. *It is worthwhile to consider broadening to include electronic health records when talking about registry-based clinical trials (this concept was mentioned by three interviewees).*

2. *What seems to be missing in the definition is what the goal of the registry, which is the "why": why do you have a registry? And the common goals for such registry programs are to measure and improve quality of care, to monitor device or medication surveillance, to support clinical research, etc. Having something about the reason the registry exists is very essential.*

3. *The only thing I would probably question is the word "Outcome." In my experience, we've used registry to collect information on demographics, they aren't always longitudinal, and sometimes they are just snapshots. They are collecting more demographic and system burden information and I think it's a broader definition than what you have here, and a broader definition is what is used by patient organizations.*

3.2 Registry Use to Facilitate Embedded Clinical Trials



The interviewees were asked if registries can be more widely used to facilitate embedded clinical trials. Although the majority (23 of 25) of responses were "yes"; there were many caveats to that "yes" response.

3.2.1 Further Thoughts from "Yes" Responders

Although they said yes, the interviewees did go on to discuss their thoughts, which fell into a few themes:

1. Primarily valuable for recruitment (of both sites and subjects)
2. Ideal in order to better design a study (e.g.: feasibility, appropriate outcomes, estimating effect size, eligibility criteria, and possibly to more cost effectively capture longer-term outcomes)
3. It is expected, and registries are conducive to, tracking long-term outcomes.

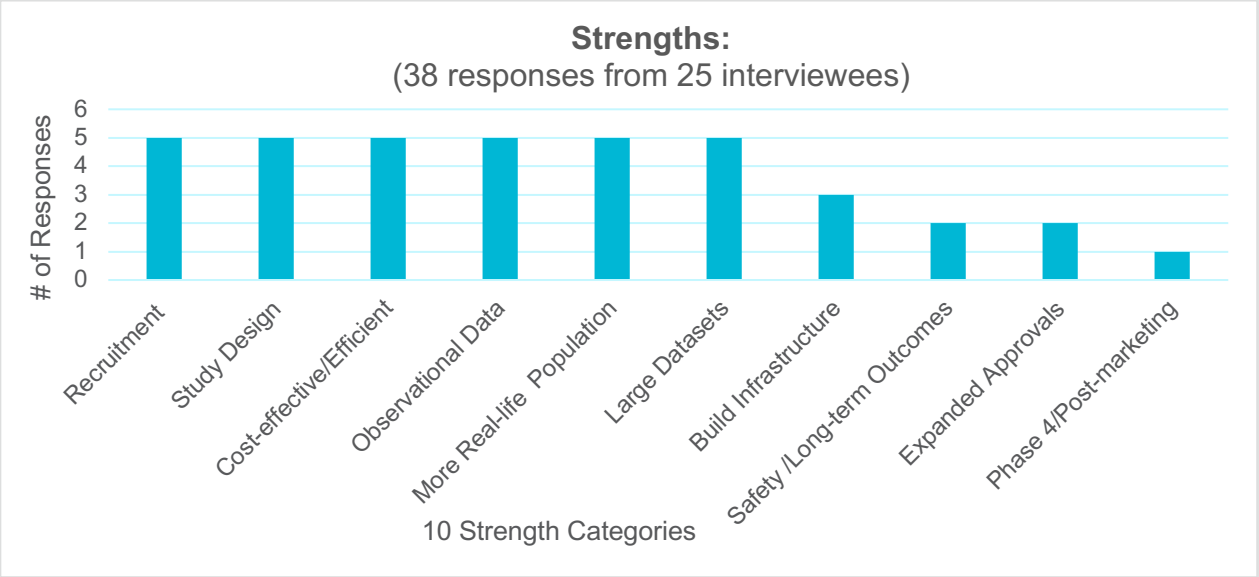
3.2.2 Rationales from "Don't know" Responders

1. *I guess I am maybe not completely convinced yet, but it also might be the fact that I don't have enough information about how they are used. I work with rare disease and it's unusual to have enough numbers in a (rare disease) registry to overcome some of the inherent variability and selection bias.*

2. *Depends, but if the overall idea is that an existing registry would be used to recruit into clinical trials, then yes.*

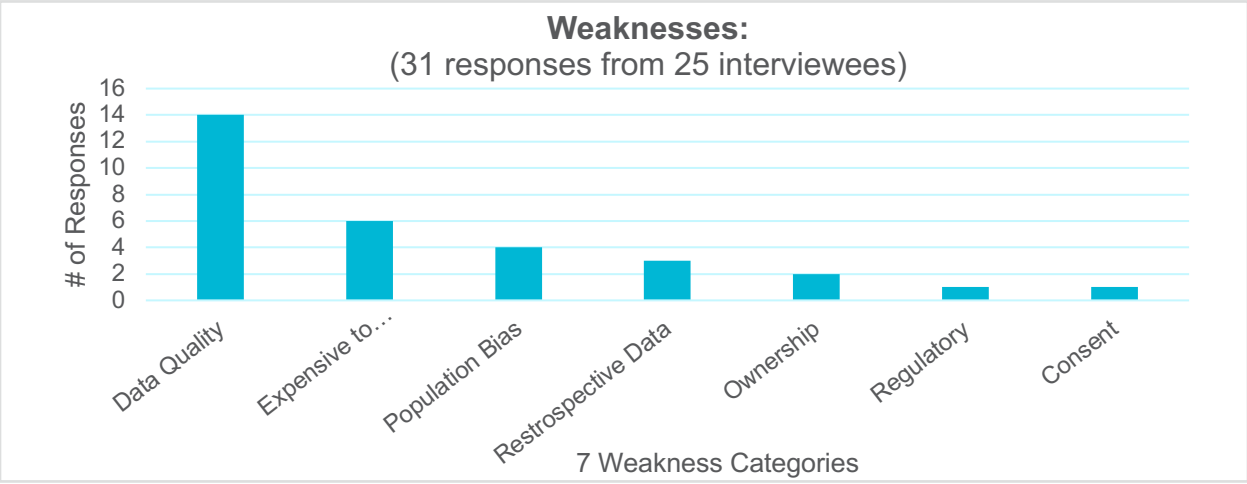
3.3 Strengths of Registries

The twenty-five interviewees listed thirty-eight "strengths," spanning ten categories. The frequency of their responses is detailed in the bar chart below. The top six responses were equally popular: facilitates recruitment, helps plan the study design, cost effectiveness of utilizing data already being collected in registries, observational data cohort, population more representative of "real life," and large datasets mean that issues with bias and data quality and less likely to be significant or impact the results.



3.4 Weaknesses of Registries

The twenty-five interviewees listed thirty-one weaknesses, spanning seven categories. The most frequent issue cited was concerns over data quality. The costs of maintaining a registry was another large area of concern. Less frequently cited were concerns of population bias, the retrospective nature of the data, figuring out data ownership arrangements, and the hurdles of consent and regulatory items.

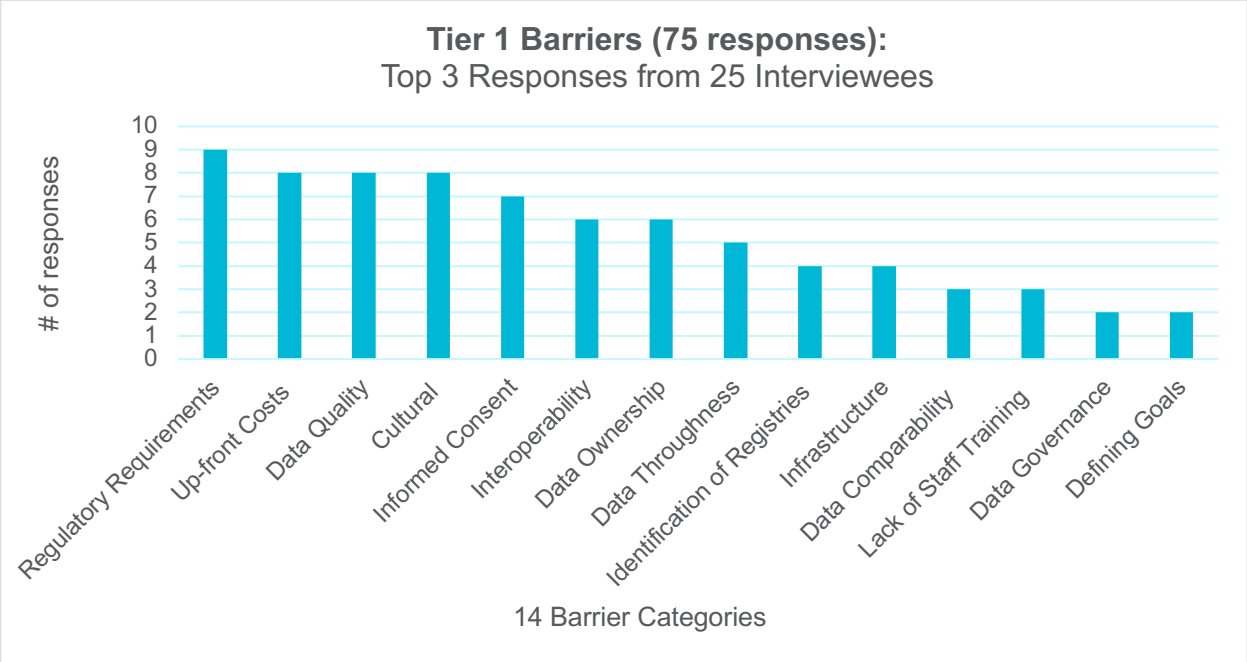


3.5 Barriers

The barriers were gathered across two questions, in order to get both a first and second tier set of barriers.

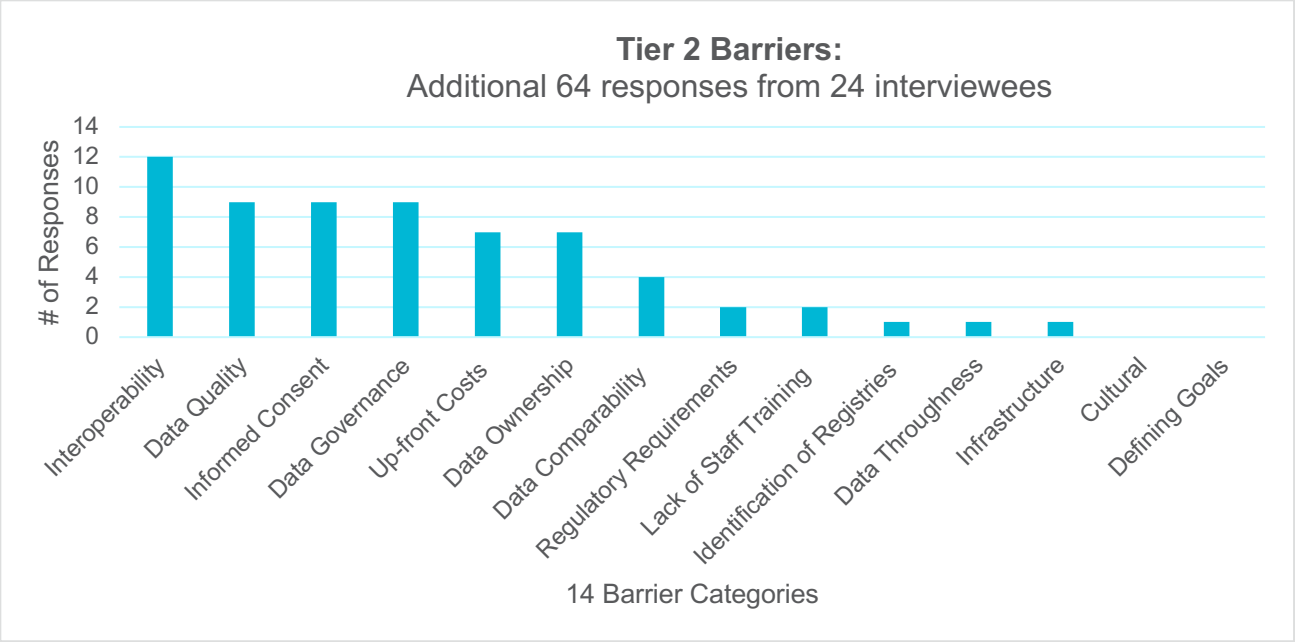
3.5.1 Top 3 Barriers (Tier 1 Barriers)

The twenty-five interviewees provided seventy-five responses for the Tier 1 barriers. They were instructed to each give three responses. The responses are given according to frequency, from left to right, in the graph below. Concerns of regulatory requirements, costs, and data quality were popular. The response of "cultural" covers the range of responses speaking to getting the research community to embrace this idea of using registry data for a clinical trial, with commentary that there needs to be some sort of education and demonstration that embedding a clinical trial in a registry will work.

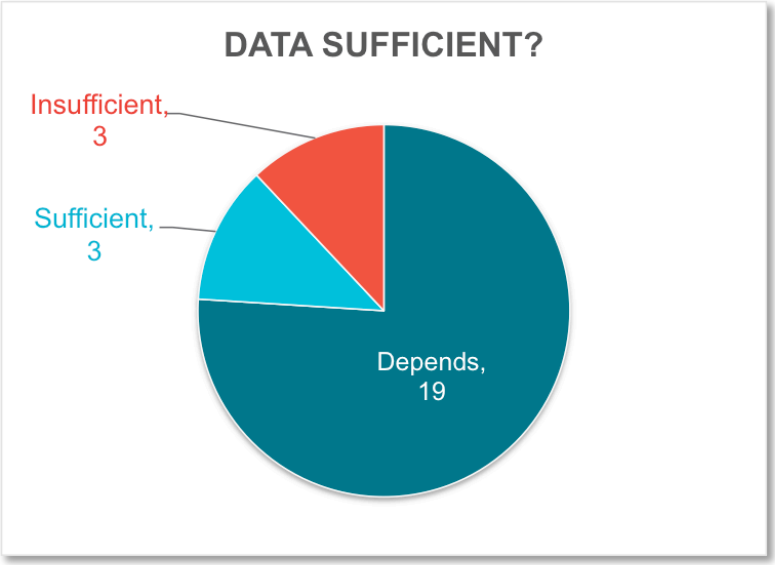


3.5.2 Additional Barriers (Tier 2 Barriers)

There are sixty-four additional barrier responses listed as a second response (one interviewer had no barriers included beyond the original three [Tier 1] that is reported above). The more frequent Tier 2 responses included interoperability, data quality, issues with informed consent, and how to handle data governance and data comparability.



3.6 Sufficiency of Data Collected in Registries



There were very few definitive responses to this question, with the majority of the responses starting with "it depends" and then defining the conditions under which they might find registry data sufficient.

An interesting highlight was given by one of the interviewees regarding how incredibly valuable longitudinal data in a registry can be, by recounting the unexpected results showing that estrogen replacement for women caused a clinically meaningful increased risk of developing coronary heart disease: "*we nearly made a disastrous mistake that would have affected 50% of the adult population; if there was ever a cautionary note about a clinical trial, this one of the best examples*."

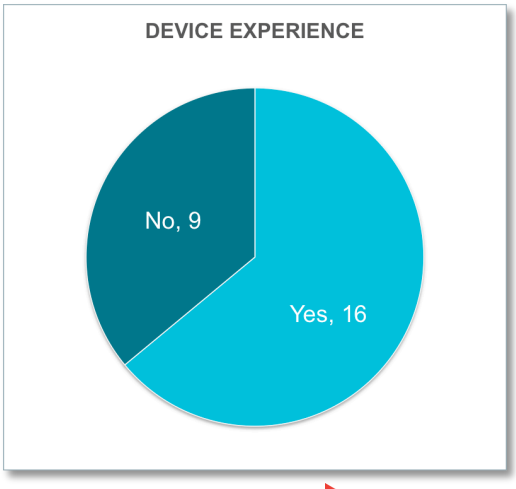
The various stipulations to "it depends" could be clustered around either study design or data quality concerns:

Sufficiency of Data (from 19 Interviewees in the "it depends" category)	
Study Design Comments:	1. *The question is not if the data collected is sufficient or insufficient, the question is if the infrastructure is flexible enough to accommodate what the clinical trial needs to measure.* 2. *It will depend on the objective of the clinical trial.* 3. *Generally not sufficient, simply because clinical trials often drive for certain endpoints that you might not find in a registry.* 4. *If you mean is it sufficient to assist in hypothesis generation for a clinical trial, I think it's reasonably secure.* 5. *It depends on the type and purpose of trial, as well as the endpoints you are collecting.* 6. *It depends solely on the study question, design, and outcomes.* 7. *It's all in the structure but can be sufficient. It depends solely on the study question, design, and outcomes.*
Data Quality Comments:	1. *If you mean for other things around extending the results of the clinical trial, I think it depends on the risk of being wrong.* 2. *It completely depends on the registry. If you aren't collecting longitudinal data it's probably not going to work.* 3. *It totally depends on if the data collected is what is needed for the clinical trial and what the quality of the data is and the monitoring.* 4. *If the sites are monitored only once every two years, then no.* 5. *Data monitoring would have to be increased, and sites trained regarding the importance of the data that is entered being used in this research way every two years, then no.* 6. *I think it could be sufficient, again you have to augment it with some additional data. It's not going to be amenable to all trials.* 7. *That depends, it could be sufficient. For medical devices, we are interested in long-term outcomes, and typical patient registries or procedural registries do not always collect long-term information.*

3.7 Device Research

3.7.1 Experience with Device Research

Overall, sixteen of the twenty-five interviewees reported having device experience. However, one of the individuals reported that they had no experience with devices, but still felt comfortable enough to respond to the device questions based on what their understanding was of the differences between drug and device research. This brought the number of interviewees who responded to these questions to seventeen.



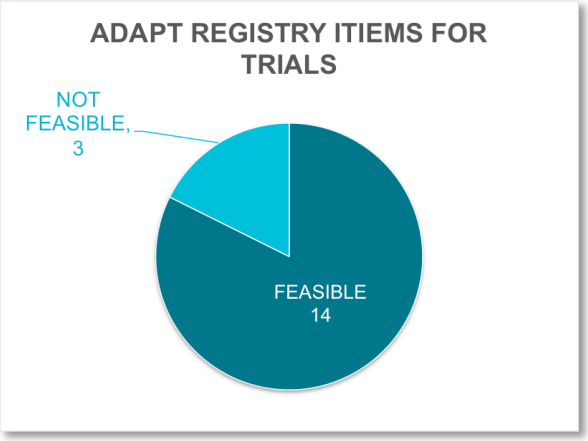
3.7.2 Differences between Device and Drug Research

In the below table, text from the interviewees is included about the differences between drug and device trials. There does seem to be more people who believe in device trials being conducted within a registry, but there are concerns on the device side with operator learning curves and the iterative aspect of devices. On the drug side, there are concerns regarding medication compliance.

Comments on Differences between Drug and Device Trials (from 17 interviewees)		
Device Trials	Experience	1. *More opportunities for devices to use registry data.* 2. *More success stories of utilizing registries on the device side.* 3. *More collaborations on effective use of registries between regulators, industry, clinical investigators, and professional societies with medical devices.*
	Learning Curve	1. *Devices have an operator learning curve.* 2. *Innovative devices have a very substantial learning curve for physicians.*
	Iterative Nature of Devices	1. *Devices tend to come and go in iterations.* 2. *Registries are ideal for picking up on the iterative development of devices, in the real world setting, and as the device evolves.* 3. *You need more information from the device trials.* 4. *Databases need to collect detailed information about the operator and the device characteristics.*
	Acceptance	1. *Greater acceptance of registries in the device world than in the drug world.* 2. *Device landscape is more willing to entertain a registry-based randomized trial for either label extension or actually labeling.*
	Regulatory	1. *Regulatory requirements for a device to be approved are lower.* 2. *Medical devices are regulated based on risk, so it's very different from drug research.*
Drug Trials	Feasibility and Benefits	1. *Drug studies may work better (since as the device evolves and there are many operator factors to consider).* 2. *Drug formulation stays the same throughout the life of that drug.* 3. *Med compliance is an issue.* 4. *There is a compliance issue that makes drug registries difficult.* 5. *Registry is a good idea for capturing adverse events and long-term clinical outcomes.*

3.8 Feasibility of Adapting Registry Tools, Regulations, and Experiences in Device or Pharmaceutical Research

The majority of interviewees did think some adaptation of registry items would work for clinical trials.



3.9 Registry Operational Adjustments for Randomized Clinical Trials

A variety of responses were gathered when asking about operational adjustments that would facilitate using registries for trials. The majority of these responses had to do with either data quality items or registry design items. Lastly, there were some regulatory and contractual items that were given as operational adjustments.

3.9.1 Data Quality

In order to ensure quality data is gathered, with an emphasis on outcomes data, comments included an emphasis on site education, standardizing data definitions, and using validated data instruments. Further discussion points included capturing adverse events and monitoring data. Along with monitoring, there were comments about the need for clear data standards and the ability to audit and edit the database.

3.9.2 Registry Design

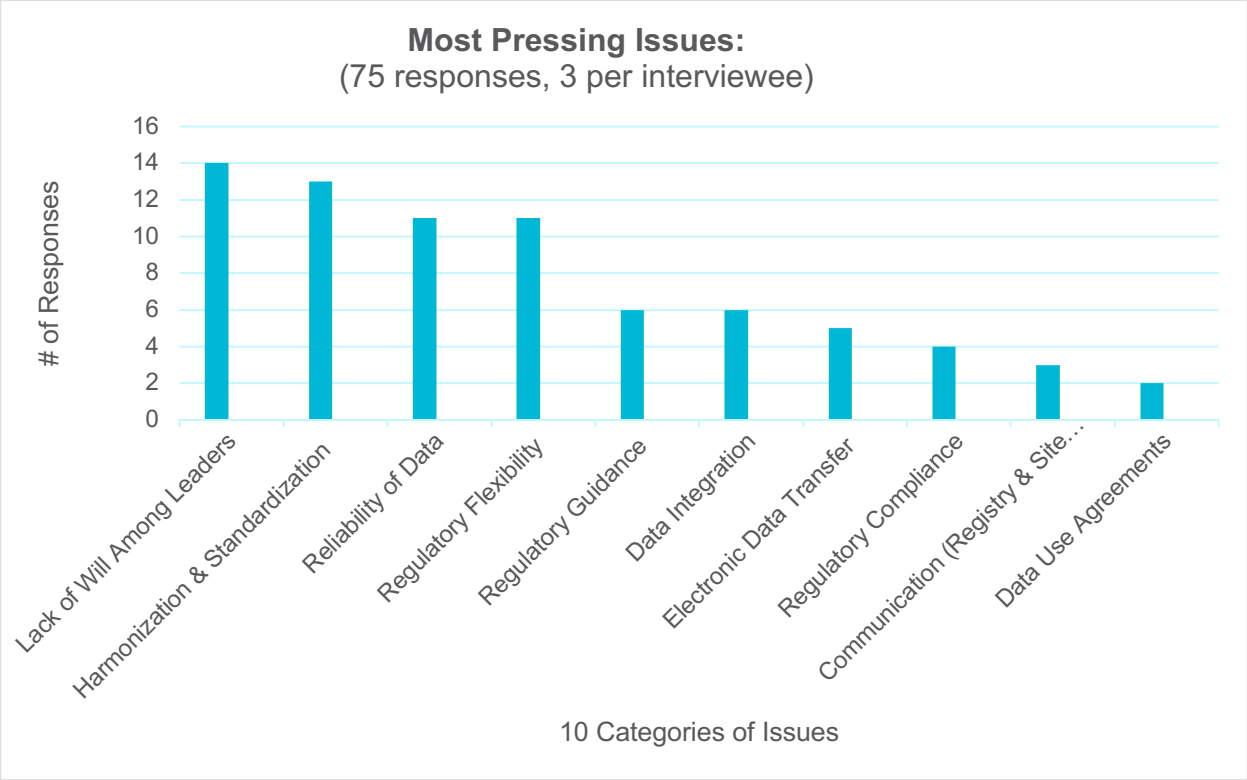
Emphasis should be on setting up registries from the beginning to be able to do trials. It should be prioritized to determine the governance structure and have that negotiated from the start of a registry. Include input from stakeholders, including individuals with trial, medical, and scientific expertise.

3.9.3 Regulatory and Contractual Considerations

Regulatory guidance needs to be provided so that registries can be designed with datasets that will be adequate to support a regulatory submission. Consent needs to be broad enough to cover being contacted about future research. The use of reliant IRBs and master contracts can help build efficiencies into being able to utilize the registry data. It will be important to have data safety monitoring committees who can adapt traditional data monitoring roles to cover this work with registry data.

3.10 Most Pressing Issues

The following chart lists the seventy-five most pressing issues the interviewees identified (three per interviewee), decreasing in frequency from left to right. Almost all of the categories could be lumped into either regulatory or data quality. Lack of will among leaders, regulatory guidance, and regulatory flexibility all speak to the need for some clear communication regarding what would be supported by the governmental agencies. It has been communicated in several different ways, but the experts recognize there will be resistance to being creative in adopting some registry approaches in their research efforts without clear direction of what is being proposed and what would be acceptable. The other pressing needs are related to data, and again go back to what will be deemed acceptable levels of evidence.



3.11 Near-term Actionable Items

There were a variety of near-term actionable items; the majority of these ideas are specific to how to better support using registry data for trials. The secondary category includes some more specific items about data and regulations.

Suggestions for supporting the development of registries:

1. *Review and build off of work AHRQ has already done with their efforts around a registry of registries, as well as a handbook and defining criteria for rating a registry.*
2. *Develop an infrastructure to support and guide groups in developing quality registries.*

3. *Registry Trial SWAT team of professionals who would go out to meet those who would be interested in accepting a registry-based trial, walk them through the process, and provide help with the logistics and statistics aspects.*
4. *Making templates available for those interested in registry research do not have to reinvent the wheel.*
5. *Creating greater awareness of what sorts of data quality the registry needs.*
6. *Identify no more than two critical forward-looking public health issues for which either a similar type of very innovative new drug or new device registry will be used, and using a limited focus a framework.*
7. *Gather stakeholders so they are all able to get on the same page to determine where it is they think registry-based randomized trial fits in the landscape of research.*
8. *Facilitating people to get registries going, offer technical support and tools to get the registry started.*
9. *It would be really good if there were more examples of successful implementation of running a clinical trial from a registry.*
10. *Survey the device and drug industries to see what their rate-limiting factors are and work on those issues.*
11. *Build large-scale registries with the ability to follow up patients and have access long-term, specifically mortality.*
12. *Harnessing of the FDA's enthusiasm and buy-in, encouraging industry to use the registry to meet their regulatory needs for device and drug approval.*
13. *Clarify how registries could be more useful in regulatory decisions.*
14. *Map of registries with key areas, with the vital information and the quality of the data.*
15. *Pilot projects that show the potential of these approaches where you can get the most done with the least risk.*
16. *Diagnostics is a true wild west. Having registries doing more long-term follow-up would help. Particularly with concerns about over diagnosis.*
17. *If FDA moves from pre-market to post-market, I think that goes hand in hand with having post-market registries, and that suggests the initial conversations with FDA about how much will be pre-market and how much will be post-market, what is going to happen in terms of a regulatory framework has real consequences.*

Suggestions for more specific data or regulatory action items:

18. *Centralized and reliant IRB.*
19. *Push on the regulatory flexibility of this collaboration idea.*
20. *Streamlining the informed consent process.*
21. *Engaging patients in understanding the importance of registry participation.*
22. *Addressing HIPAA restrictions through guidance and regulatory flexibility.*
23. *Payment would be contingent on participation in an accompanying registry.*
24. *Using identical pre-specified data elements with standardized definitions.*

3.12 Longer-term Actionable Items

The responses to suggestions for longer-term action items also ended up being able to be categorized, this time into three categories: development of registries, costs, and data items.

Support for supporting the development of registries:

25. *Build a sociocultural environment that will promote opportunities to share, and increase the awareness and the willingness to work for the common good.*
26. *A top down embracing of registries which includes promoting, advertising, and encouraging the registry of registries.*
27. *Develop a national 'plug and play' registry infrastructure.*
28. *Regulatory guidance so it is less risky.*
29. *Some type of quality ranking for registries.*
30. *Getting everybody to use the same data platform across the board.*
31. *Education to increase collaboration across diseases, and then to get the word out about registries.*
32. *Regulatory legislation to start building collaborations with regulatory authorities and legislation that will allow registry trials to be performed.*
33. *Mandate that phase 4 trials are done through registries.*
34. *Regulatory pathway for rapid review, or priority review, if doing a clinical trial from a registry.*

Suggestions for data action items:

35. *Probably the data interoperability piece. It will be a tougher goal to achieve.*
36. *Standardization and interoperability of a common platform nationally.*
37. *Data use agreements (all of those IRB type of issues that are quite cumbersome and especially if you are using registries from multiple places).*
38. *Real-time notification, to instantly know when a patient meets the inclusion criteria for potential clinical trial that is being conducted.*
39. *Use of the EMR, auto-populating data issues, and a nationally coordinated registry network.*
40. *More efficient data model to better incorporate EMRs, claims data, and physician reporting into a much more efficient and continuously running registry platform.*
41. *Get the people who do registries together to talk about what kind of endpoints are suitable for a registry without a large modification.*
42. *Acknowledgement that what is collected in electronic health records is going to be controlling what data is going to be used for registries, and ensure that there is harmonization with the data elements.*
43. *Get people to agree to data standards and data sharing agreements.*
44. *National unique personal medical identifier, separate from the social security card, to be able to track outcome of individual patients using EMR.*

Costs:

45. *One of the chief concerns with registries is making them self-sustaining, they are expensive.*
46. *Government legislation that actually would put funding to provide for maintaining registry infrastructure at the national level.*
47. *Address the methods and cost sharing implications of long-term follow-up.*

3.13 Additional Feedback from Interviewees

48. *So I'm hopeful that in the next couple of years as these things start to unfold, that maybe we can show in a micro environment that we've got it, and it can be done, and the regulatory body is satisfied with it.*
49. *I think researchers are stuck in the ideal design, and they don't want to jeopardize a regulatory submission with data they fear is perhaps inadequate, and they want to have greater control.*
50. *If you don't know about this registries handbook we did for AHRQ, it's going into its fourth edition and widely used. The first issue was in 2007, so a lot has gone into registry science and codifying it and making it ready for prime time. The book is written and in two volumes. We're ready, the time is now. You have to apply quality standards to registries that are appropriate for registries.*
51. *I think people aren't as used to registries, they are hard to get funded and keep funded, and the quality isn't that great because people aren't used to doing them.*
52. *Improvement also needs to be made to areas such as issues dealing with sociocultural, and collaboration across different institutes and states.*
53. *There are ways to streamline, to make it more user friendly for patients, investigator, manufacturers, and facilities.*
54. *It's not about just how to do the traditional randomized clinical trial. But it's to open how to use registries in a broad way, in clinical development. Because other opportunities exist; for instance, registries as external comparative for a single arm clinical trial.*
55. *Two things come to mind. One group we didn't really mention were the electronic health record companies. I'd also talk with folks who set up the NCI MATCH trial and see what they did to try to get some alignment across companies with common protocols. This approach lends itself to an enduring protocol. If you have common protocol that you can role modules in to or out of, that would be powerful.*
56. *Leverage some of the existing work that has been done, particularly with devices. I think that's the merit of collaborating, resources are limited and folks would like to create something that's value added.*
57. *I am skeptical of the ability of non-systematically collected data being used to answer clinically relevant questions. There are too many examples of observational data that has been turned around when the clinical trial is done. There is a lot of potential to be creative and efficient in thinking about how we can combine data from observational data from registries with clinical trials, but it needs to be clearly thought through with some very specific questions in mind.*
58. *There is the idea of people that participate in registries and people that don't. I think we really do need to be thinking about collecting information from those that don't participate (population bias).*
59. *When I look at these questions I feel like the patient perspective is missing and the issue of consent isn't in the choices for what do you think are issues, it depends on who you talk to on what are issues. Reaching out to the patient community on this and making sure when we come up with recommendations for registries that we didn't think of this in a narrow fashion.*

3.14 Key Points

There is little doubt among the experts that more can be done with registry data. However, there is some doubt that there will be robust enough registries that can support an embedded clinical trial, like what was accomplished with SAFE-PCI, beyond the larger disease groups (for instance cardiology, oncology, diabetes, maybe some broader groups of ailments like kidney disease).

As a starting point, there does seem to be consensus that clear guidance on what will be acceptable to use in a regulatory submission, as well as an effort to spread the word about the importance and increased use of registry data will help to alter the importance placed on registries.

Another reoccurring suggestion was for more information and guidance to be given to help identify quality registries and develop a registry that will be high quality going forward.

A final area to consider for prioritizing efforts would be to work on developing data guidance, including how to train those working on registries, and then how to monitor the registry data that is collected.

Appendix A. TABLE OF INTERVIEWEES

	Name	Affiliation
1	Ron Bartek	Friedreich's Ataxia Research Alliance (FARA), National Organization for Rare Disorders (NORD)
2	Elise Berliner	Agency for Healthcare Research and Quality (AHRQ)
3	Ralph Brindis	American College of Cardiology (ACC)
4	Greg Daniel	Brookings Institution
5	Chris Dowd	Cystic Fibrosis Foundation
6	Nancy Dreyer	University of North Carolina and Quintiles
7	Ole Frobert	Orebro University Hospital, TASTE Research Team
8	Sharon Hesterlee	Myotonic Dystrophy Foundation
9	Louis Jacques	ADVI (Healthcare Advisory Services Firm)
10	Stefan James	Uppsala Clinical Research Center, TASTE Research Team
11	Javier Jimenez	AstraZeneca
12	Jeffrey S. Kasher	Patients Can't Wait, LLC
13	Mitchell Krucoff	Duke Clinial Research Institute, SAFE-PCI Research Team
14	Beverly Lorell	King & Spalding, LLC
15	Danica Marinac-Dabic	Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH)
16	Evan Myers	Duke University, COMPARE-UF Fibroid Registry
17	Sharon-Lise Normand	Harvard University, Department of Health Care Policy and in the Department of Biostatistics
18	Bray Patrick-Lake	CTTI, NIH Precision Medicine Initiative
19	Rich Platt	Harvard University, Department of Population Medicine
20	Sunil V. Rao	Duke Clinical Research Institute, SAFE-PCI Research Team
21	Kristen Rosati	American Health Lawyers Association (AHLA)
22	John Rumsfeld	American College of Cardiology (ACC)
23	Bob Temple	Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER)
24	Carol Ann Wallace	University of Washington School of Medicine and Seattle Children's Hospital, CARRA Registry
25	Bram Zuckerman	Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH)

Appendix B. BACKGROUND INFORMATION FOR EXPERT INTERVIEW

CTTI REGISTRY TRIALS PROJECT
BACKGROUND INFORMATION FOR EXPERT INTERVIEW
(September 17, 2015)

The Clinical Trials Transformation Initiative's (CTTI) Registry Trials Project (RTP) focuses on the opportunity to increase efficiencies and decrease costs of research by embedding clinical trials within registries, for both pre- and post-marketing clinical trials.

Current barriers and gaps include:

1) Identifying appropriate registries;
2) Ensuring data quality/comparability;
3) Meeting variable regulatory/legal requirements;
4) Protecting privacy/security; and
5) Clarifying the processes needed to implement a registry-based clinical trial.

For this project, we are using an adapted version of the EMA's (European Medicines Agency) *definition of registries:*

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 -- such as a disease registry -- or prescription of a drug, device, or other treatment -- such as an exposure registry.

Some examples of published embedded registry trials are TASTE: Thrombus Aspiration in ST-Elevation Myocardial Infarction and SAFE-PCI for Women: Study of Access Site for Enhancement of PCI for Women Trial.

PLEASE REVIEW THE FOLLOWING QUESTIONS BEFORE YOUR INTERVIEW

1. Is the above EMA definition similar or different to your own thoughts about a registry? If different, how is it different?

2. Do you feel registries can be more widely used to facilitate embedded clinical trials? Why or why not?

3. What do you feel are the major strengths or weaknesses of registries that make them suitable for facilitating randomized clinical trials?

4. Please describe what you believe are the top three barriers to embedding a randomized clinical trial within an existing registry. What do you think are potential solutions to address those barriers?

5. Aside from your top three barriers, I will read you a list of other barriers identified by our Project Team. Which three of these barriers do you also believe are major barriers and what potential solutions do you think could overcome them? (Only choose barriers that were not used in your response to the previous question.)
    a. Regulatory requirements
    b. Up-front costs
    c. Interoperability (the ability for multiple systems to exchange and interpret information)
    d. Identification of appropriate registries
    e. Ensuring data quality
    f. Lack of staff training
    g. Informed consent
    h. Data governance
    i. Data ownership

6. Do you think the data collected in a patient registry is sufficient or insufficient to support a clinical trial? Why?

7. Now, I would like to hear your thoughts on the use of registries, specifically within the device sector.
   IF NOT ALREADY KNOWN, Do you have experience in the device sector?

   YES → GO TO Q8
   NO → GO TO Q10

8. In the device sector, there are several examples where registries have been utilized effectively for clinical trials. How do you think the device landscape is different from the drug landscape with respect to utilizing registries?

9. Do you think it is feasible or not feasible to adapt the tools, experiences, and/or

regulations, used in registries, for device trials or randomized drug trials?

10. What operational adjustments do you think need to be made to registries, so they could be used for randomized clinical trials?

11. Please identify which three issues you feel are the most pressing and what potential solutions there may be to those issues. Of the remaining issues which you didn't identify as 'most pressing,' are there any others to which you can offer potential solutions?
    a. Harmonization and standardization
    b. Reliability of data
    c. Regulatory flexibility
    d. Regulatory guidance
    e. Lack of will among relevant leaders
    f. Data integration
    g. Data use agreements
    h. Electronic transfer of data from registry to a case report form and/or pharmaceutical company databases
    i. Communication between registry personnel and site coordinators
    j. Regulatory and/or company-specific (e.g., SOPs) compliance

12. If you could make ONE *near-term* ACTIONABLE change for increasing the use of registries in randomized clinical trials, what would it be? Why?

13. If you could make ONE *longer-term* ACTIONABLE change for facilitating the use of registries in randomized clinical trials, what would it be? Why?

14. Is there any topic that you would like to expand on or anything that we haven't covered that you believe is important?