

CTTI RECOMMENDATIONS: REGISTRY TRIALS

INTRODUCTION

Depending on its characteristics and capabilities (e.g., interoperability, connectivity, flexibility, sustainability), a registry¹ can be used either as an observational data source for generation of clinical evidence and hypothesis generation, or as a critical reusable component of the clinical trial infrastructure within which prospective randomized studies can be performed. Information collected in clinical observational registries, such as medical history, demographics, disease diagnosis, and outcomes data, often overlap with data gathered for clinical trials. Thus, integrating clinical trials within such registries may offer opportunities to 1) avoid duplicative data collection, 2) Identify and recruit patients more efficiently 3) reduce time to database lock, and 4) accelerate time to critical decision-making, while 5) potentially reducing clinical trial costs. Questions exist, however, regarding whether registries can satisfy data quality requirements for regulatory decision-making, and whether they are able to support randomized trials.

Although it appears there is a clear role for registries in creating a sustainable infrastructure within which clinical trials for regulatory submissions can be conducted, standards and practical considerations have not been defined for the use or modification of existing registries or the design of new registries to make them fit for conducting clinical trials. Such standards are essential for consistent evaluation of a registry's suitability for generating the clinical evidence needed for regulatory decision-making in the various phases of drug and device development. Our purpose is to provide recommendations for registry assessment and design that would facilitate determination of a registry's suitability for conducting embedded clinical trial intended for regulatory submissions.² However, we encourage researchers and those engaged with registry development to interact with regulators to ensure that such data are acceptable for regulatory submission.

¹ A registry is 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. At their core, registries are data collection tools created for the purpose of generating clinically usable information and evidence. 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). This definition is an adapted version of the European Medicines Agency's definition of *registry*.

² We recognize that registries are successful tools to facilitate clinical trials and should continue to be used for activities such as: identifying and recruiting patients, trial feasibility assessments, and reducing the amount of baseline and/or follow-up data that needs to be collected for a clinical trial.

RECOMMENDATIONS

FOR EXISTING REGISTRIES:

To determine if an existing registry is appropriate for embedding clinical trials, we recommend the following:

- 1) Assess whether the historical evidence generated by an existing registry has demonstrated the reliability, robustness, and relevancy necessary to provide a platform for collecting data in an embedded clinical trial to support regulatory decision-making, with assurance of patient protections (see [Decision Tree 1](#) and [Table 1](#)).
- 2) Assess if an existing registry contains the elements needed to support a randomized clinical trial. Satisfaction of all the following requirements suggests that the existing registry, together with any appropriate configurable elements, may provide high-quality evidence suitable for regulatory decision-making (see [Decision Tree 2](#) and [Table 2](#)):
 - a. Are the data previously generated by the baseline registry historically regarded as robust and reliable (i.e., high-quality data)?
 - b. Can the baseline registry and its dataset provide the core data needed to answer the question at hand (i.e., relevant or fit for purpose)?
 - c. Can any processes or data not provided by the baseline registry be added or the registry reconfigured to accommodate these needs (e.g., programming to allow identification of suitable trial participants or documentation of informed consent, modular add-on datasets or linkages to other databases, and appropriate data accessibility with maintenance of patient and data privacy)?

FOR NEW REGISTRIES:

To design a new registry suitable for embedding clinical trials, we recommend following software industry guidelines, as well as guidance documents provided by regulatory agencies, to assure that the registry complies with both industry and regulatory standards (see [Table 3](#)).

► These recommendations are based on results from the [Registry Trials Project](#).
► CTTI's [Executive Committee](#) approved these recommendations.
► Released May, 2017

DECISION TREE 1: EXISTING REGISTRY – HISTORICAL ASSESSMENT

Evaluate if historical evidence generated by an existing registry is robust, relevant, and reliable, with assurance of patient protections

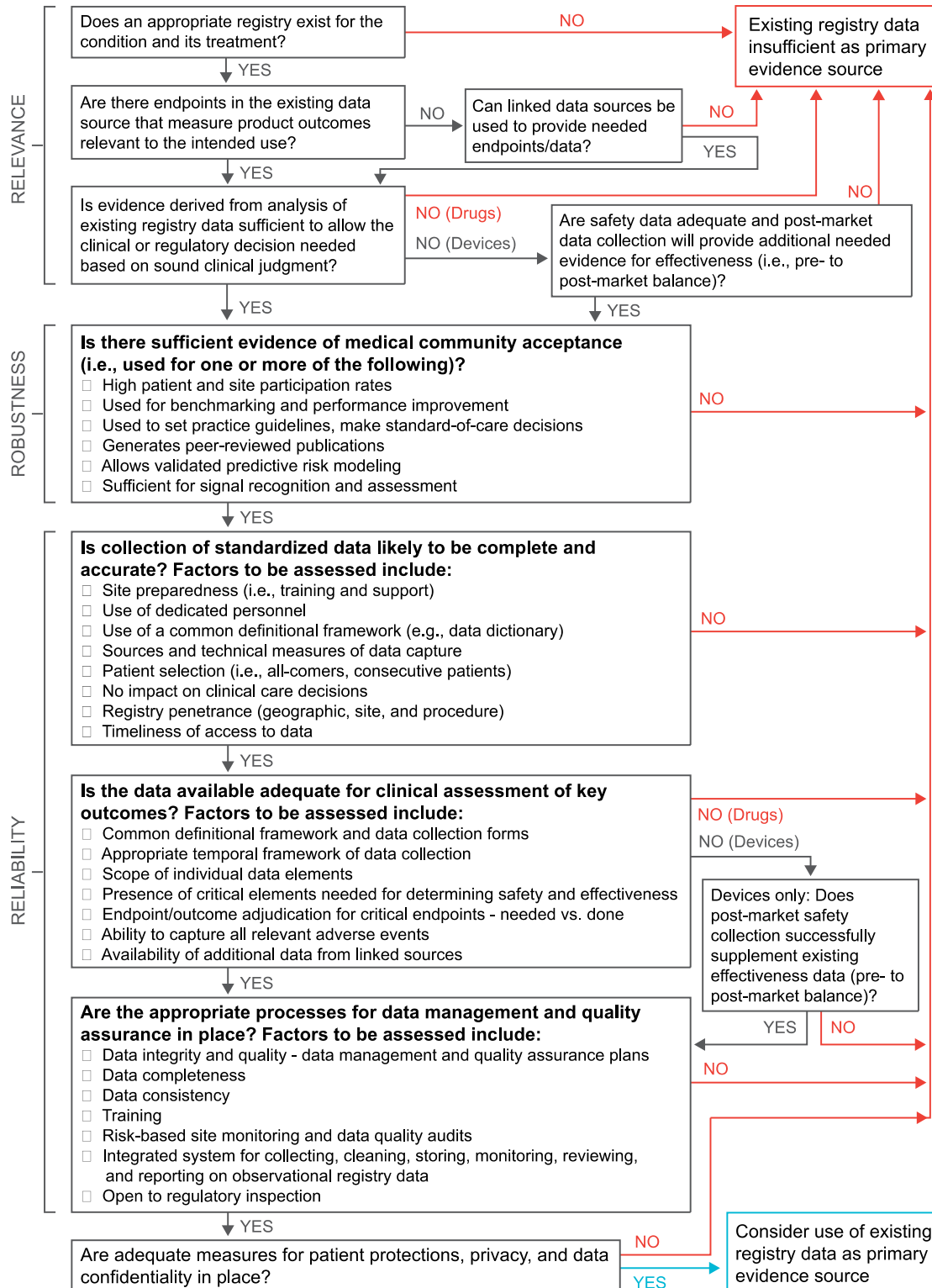


TABLE 1: EXISTING REGISTRY – HISTORICAL ASSESSMENT

Evaluate if historical evidence generated by an existing registry is robust, relevant, and reliable, with assurance of patient protections

Table 1 provides greater detail of the pathway laid out in Decision Tree 1.

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must demonstrate relevancy and robustness to support regulatory decision-making	<p>Data are relevant:</p> <ol style="list-style-type: none"> 1. Data are adequate in scope and content 2. Data are generalizable: Registry reflects high site and patient participation rates compared with total population <p>Data are robust—acceptable for use in one or more of the following:</p> <ol style="list-style-type: none"> 1. Validated risk prediction 2. Quality assurance 3. Performance improvement 4. Benchmarking 5. Informing practice guidelines 6. Post-market surveillance 7. Generating peer-reviewed publications 8. Comparative effectiveness research 	<ul style="list-style-type: none"> ▶ Evaluate if data generated by an existing registry are adequate for evaluating clinical outcomes or supporting regulatory decision-making ▶ Assess whether data and evidence that are generated can address the question at hand (i.e., fit for purpose) ▶ Connectivity: Establish whether there are linkages, or the ability to link to other existing datasets for additional data not captured directly in the registry ▶ Data should be suitable for adequate statistical analysis ▶ Data should be interpretable, i.e., evidence derived from analysis of de-identified aggregate data should be sufficient to allow for regulatory decision-making
Registry data must reliably be able to support regulatory decision-making	<p>Design: The registry should be designed to capture reliable data from real-world practice (no protocol-driven treatment)</p> <p>Patient population: The patient population should be limited to those with specific diseases, conditions, or treatment exposure(s)</p>	<ul style="list-style-type: none"> ▶ A standard operating procedure document should exist that defines the processes and procedures for data capture and management ▶ The system should have a basic validation package to assure that the software acts as intended ▶ The patient population for the registry is associated with a specific disease, condition, family of procedures (e.g., orthopedic surgery), or treatment exposure(s) ▶ Inclusion and exclusion criteria should be clearly defined (e.g., total population or population subset)

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must reliably be able to support regulatory decision-making <i>(continued)</i>	Data collection forms: The data collection forms should be standardized	<ul style="list-style-type: none"> ▶ The existing data elements should be fixed and predefined ▶ There should be an audit trail for any changes ▶ The forms should use standard and uniform data definitions
	Datasets: Data elements should be able to be mapped to industry standards to allow for more direct comparison of data analyses	<ul style="list-style-type: none"> ▶ Documentation should be available that describes the data elements and datasets
	Timing of endpoints/outcomes: The timepoints of each endpoint/outcome in the data collection form should be documented	<ul style="list-style-type: none"> ▶ Evaluate the ability to calculate timing of treatment and treatment outcome (e.g., stroke at discharge or at 30 days post index procedure)
	Timing of data collection: Data collection/entry can occur at any time	<ul style="list-style-type: none"> ▶ The system should be live 24/7 and web-based
	Data completeness and accuracy: Data should be complete, accurate, and attributable	<ul style="list-style-type: none"> ▶ Missing data should be minimized and statistically assessed ▶ Assure processes are in place for data collection and entry with documented training ▶ The system should allow identification of the data originator (e.g., person[s] performing procedure[s]), data source (e.g., point of care, EHR, procedural record), and data entry person ▶ Data logic checks should be included at the time of data entry ▶ Processes should be in place to assure accuracy of the data
Registry has assurance of patient protections	<p>Documentation of informed consent or IRB waiver of informed consent is needed for access to the data (e.g., by investigators, patients, regulators)</p> <p>Patient privacy must be assured: Assess for use of de-identified data vs. line-item data (informed consent is required for line-item data)</p>	<ul style="list-style-type: none"> ▶ Access to the data needs to be supported by patient informed consent or IRB waiver of informed consent ▶ Use a single IRB of record where possible with a broad-use informed consent document ▶ Data encryption and security protections should be in place ▶ Control/ownership of proprietary data should be addressed

DECISION TREE 2: EXISTING REGISTRY – SUITABILITY ASSESSMENT*

Evaluate elements in an existing registry needed to conduct a clinical trial

*Decision Tree/Table 1 assessment must be made before Decision Tree/Table 2 assessment.

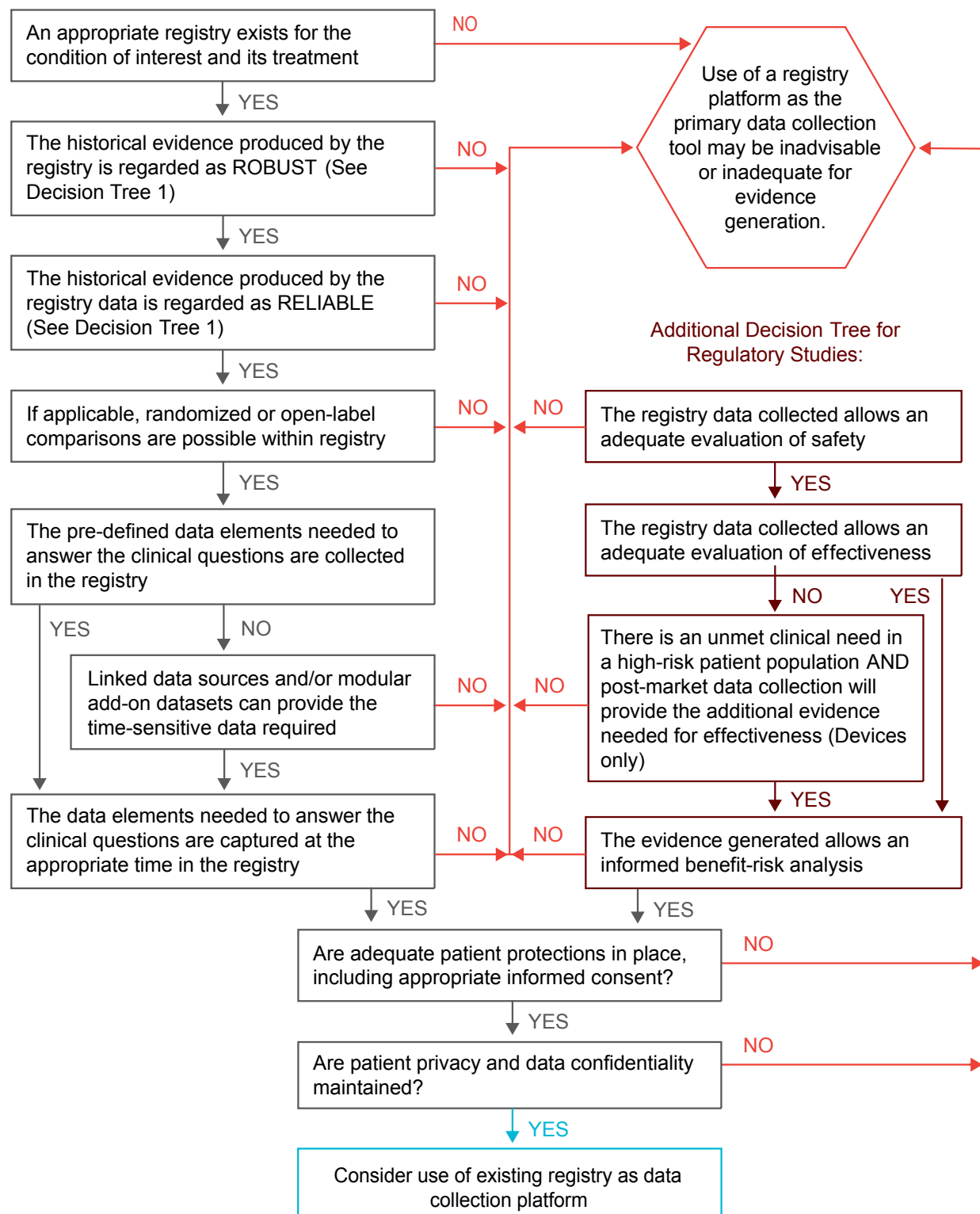


TABLE 2: EXISTING REGISTRY – SUITABILITY ASSESSMENT*

Evaluate elements in an existing registry needed to conduct a clinical trial

Table 2 provides greater detail of the pathway laid out in Decision Tree 2.

*Decision Tree/Table 1 assessment must be made before Decision Tree/Table 2 assessment.

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry must be able to support the proposed clinical trial	<ol style="list-style-type: none"> 1. The existing registry is appropriately focused on the patient population, disease and intervention of interest 2. Historically, the evidence collected within the registry is robust (see Table 1) 3. Historically, the evidence collected within the registry is reliable (see Table 1) 	<ul style="list-style-type: none"> ▶ See Table 1 for recommended assessment of a registry for use as the data collection platform for conducting prospective randomized clinical trials, including assessment of applicability, strengths, and weaknesses based on historical use
Registry data must be fit for purpose (relevant)	<ol style="list-style-type: none"> 1. Assignment of therapy: Processes must be integrated for identification, assignment, and documentation of eligible participants 	<ul style="list-style-type: none"> ▶ Assess ability to incorporate methods required for identification of study-appropriate patients ▶ Evaluate ability to embed processes for randomization into registry workflow ▶ Evaluate ability to embed processes for assurance and documentation of informed consent
	<ol style="list-style-type: none"> 2. Adequacy of data: Assure available data elements collected in the registry generate the information/evidence needed to answer the question at hand 	<ul style="list-style-type: none"> ▶ Supplement missing and/or longitudinal data elements needed for evidence generation through the use of modular add-on datasets or linkages to other datasets ▶ The eventual goal should be linkage to the EHR for procedural and long-term data collection and incorporation of data collection into the normal workflow
	<ol style="list-style-type: none"> 3. Ensure availability of appropriate data and analysis tools 	<ul style="list-style-type: none"> ▶ Identify analysis tools necessary to allow the data collected within the registry to generate interpretable results (i.e., evidence) <ul style="list-style-type: none"> • Develop pre-specified endpoints and a statistical analysis plan • Consider suitability of the totality of the data (i.e., body of evidence supporting the clinical benefit-risk assessment)

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data must be of sufficient quality (reliable) to support a prospective clinical trial	1. Data collection must be sufficient to support regulatory decision-making	<ul style="list-style-type: none"> ▶ Assess the adequacy of the registry's data collection form as a case report form (CRF)
	2. Data should be complete and accurate	<ul style="list-style-type: none"> ▶ Assure appropriately-trained personnel are available at study sites for data collection and abstraction ▶ Registry should incorporate use of a uniform data dictionary ▶ Registry should incorporate appropriate defined timing for collection of key data points
	3. Employ adequate data quality assurance procedures	<ul style="list-style-type: none"> ▶ Assess the need for enhanced auditing and monitoring of data to assure completeness and accuracy
	4. Establish processes for accountability of study subjects	<ul style="list-style-type: none"> ▶ Minimize patient withdrawals ▶ Minimize patients lost to follow-up
	5. Source data should be available for key data elements; site-reported data without independent assessment may not provide enough accuracy for key outcomes in randomized trials	<ul style="list-style-type: none"> ▶ Use independent assessors for key data, such as: <ul style="list-style-type: none"> • Independent blinded core labs when needed for data interpretation • Clinical Events Committee when needed for adjudication of key outcomes and adverse event data
Registry data and evidence generated must be accessible, with adequate provisions for patient privacy and data confidentiality	1. Establish data availability to the sponsor and/or clinical investigators, with considerations for patient privacy and data confidentiality	<ul style="list-style-type: none"> ▶ Assure informed consent adequately describes data accessibility and maintenance of patient privacy and data confidentiality ▶ Assure accurate identification of all study-enrolled patients within registry ▶ Assure ability to sequester records of study-enrolled patients (i.e., patient privacy and data confidentiality) ▶ Define timing and timeliness of sequestered record transfer for sponsor (i.e., product specific proprietary data) ▶ Define timing and timeliness of data transfer to analytic data set
	2. Ensure availability of line-item data to regulators	<ul style="list-style-type: none"> ▶ Define timing and timeliness of data and analysis transfer to regulators

REQUIREMENTS	RECOMMENDATIONS	SUGGESTED GOOD PRACTICES
Registry data and evidence generated must be accessible, with adequate provisions for patient privacy and data confidentiality <i>(continued)</i>	3. Establish necessary associations to other data sources	<ul style="list-style-type: none"> ▶ Determine and provide the necessary linkages to other registries, administrative or government databases, EHRs, etc. ▶ Identify new records generated in linked databases for longitudinal follow-up of patients enrolled in research studies
	4. Develop plan for data dissemination	<ul style="list-style-type: none"> ▶ Define timing and timeliness of data transfer to the study sponsor(s) for dissemination of outcome analyses to study participants and participating physicians ▶ As appropriate, define process for release of data and analyses to other stakeholders (e.g., ClinicalTrials.gov, payers, etc.)

TABLE 3: DESIGNING A NEW REGISTRY

Designing a new registry with the capability of embedding a clinical trial suitable for regulatory decision-making

REQUIREMENTS	RECOMMENDATIONS
Clearly articulate the concept of the registry in a transparent manner	The registry design document should articulate the vision, mission, reason, and value proposition of the registry
Define and describe participant characteristics	<ol style="list-style-type: none"> 1. The registry must minimize barriers for inclusion, thus maximizing inclusion of those having the disease/condition to be studied 2. The registry must allow for disparate treatment modalities, including drugs, biologics, devices, and combination products
Select clinically relevant data elements	<ol style="list-style-type: none"> 1. Data elements should efficiently capture and convey information in order to provide evidence based on meaningful clinical endpoints and outcomes 2. Definitions used for data elements should conform to recognized standards and nomenclature 3. There must be the ability to: <ul style="list-style-type: none"> ▶ document informed consent ▶ document randomization/assignment of patients ▶ configure/add additional data elements 4. There should be the ability to: <ul style="list-style-type: none"> ▶ identify clinically eligible patients for trial participation ▶ accept external data if not collected in the registry (e.g., EHR, reliable external datasets) ▶ measure product performance ▶ document adjudication or core lab determinations for key trial outcomes
Data collection processes must be systematic, consistent, reproducible, and reliable	<ol style="list-style-type: none"> 1. The registry must be 21CFR Part 11 compliant 2. Data traceability must include attributability of data originators and data entry personnel, with date and time stamps for all transactions 3. Data should be usable for clinical care purposes 4. Data collection should be integrated into the process of care 5. All processes must be supported by documented training and education of those entering data (e.g., data managers, data entry personnel, and registry participants)

REQUIREMENTS	RECOMMENDATIONS
Assure the registry conforms to informatics standards	<p>The registry should support:</p> <ol style="list-style-type: none"> 1. Publication of the data dictionary 2. Defined and semantic interoperational data elements 3. Use of common data elements/controlled vocabularies 4. Use of a common data model 5. Use of the FDA's Unique Device Identifier (UDI), if device 6. Referential integrity via use of single source (e.g., RxNorm, GUDID)
Evaluate and assure data quality across multiple dimensions	<p>The data must be contemporaneous, accurate, legible, consistent, complete, and reliable</p>
Patient protections must be assured	<p>Assure patient protections by including the following elements:</p> <ol style="list-style-type: none"> 1. Documentation of appropriate informed consent 2. Data confidentiality policies 3. System security compliance and security audits 4. Published explanation of intentional data uses 5. Training of data originators (i.e., data entry personnel) and managers 6. IRB oversight and review
Assure registry design is valid across multiple stakeholder analyses	<ol style="list-style-type: none"> 1. Data should support pre- and post-market regulatory as well as other stakeholder evidentiary needs 2. Data ownership and access to trial-specific data should be established prior to the start of an embedded trial (e.g., processes for sequestration of trial data from the full registry data and access limitations prior to product approval) 3. For site-based users, the registry should support: <ul style="list-style-type: none"> ▶ Quality assurance and performance improvement ▶ Risk reduction ▶ Benchmarking based on risk-adjusted outcomes 4. Anticipate distributed query and aggregate analysis
Incorporate patient-reported information within the registry	<ol style="list-style-type: none"> 1. Provide guidelines for participants in reporting to the registry 2. Provide technologies/structures to support the systematic, periodic query of participants