



Thinking Outside of the Box: Real World Data for Ultra-rare Disease Studies

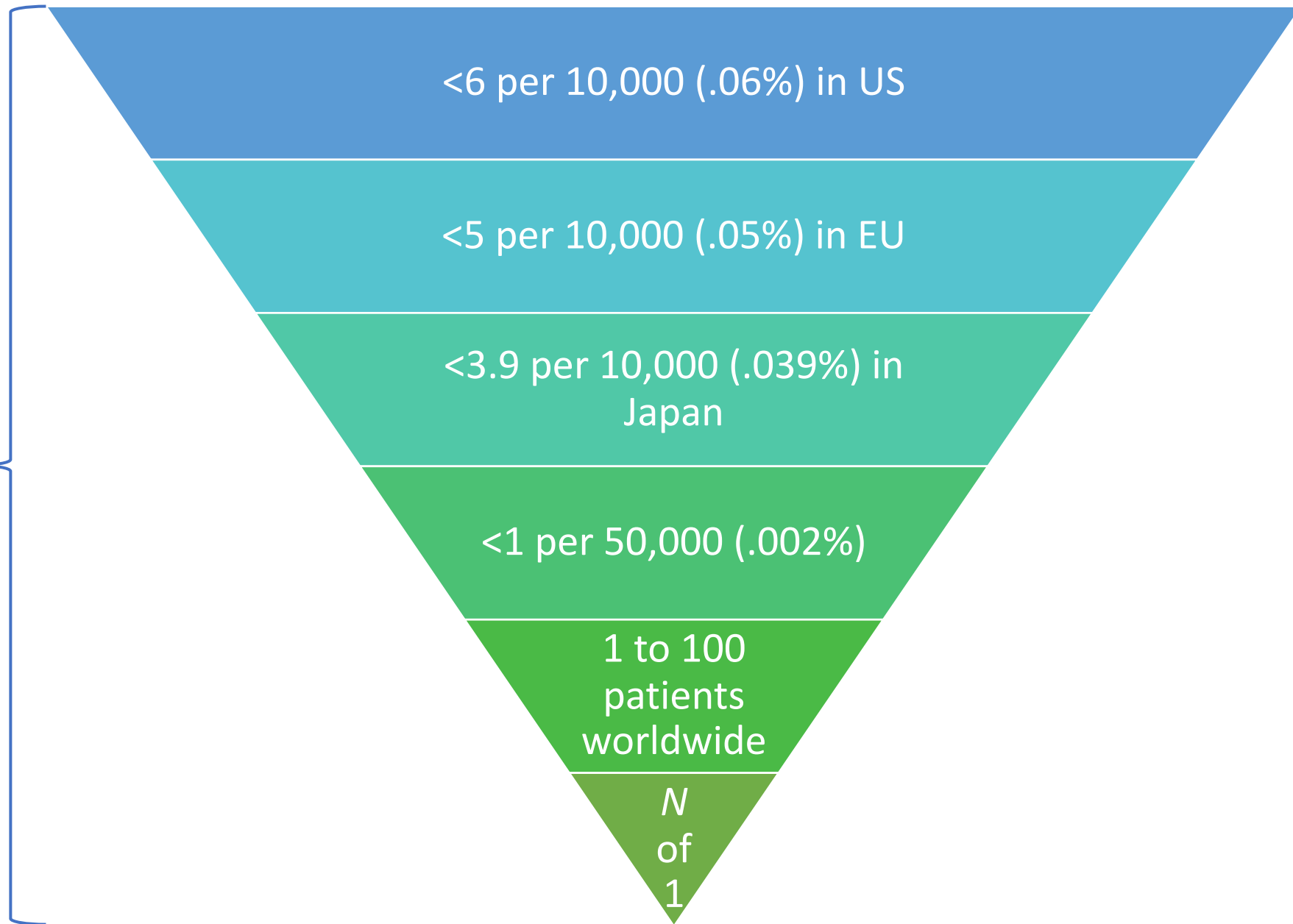
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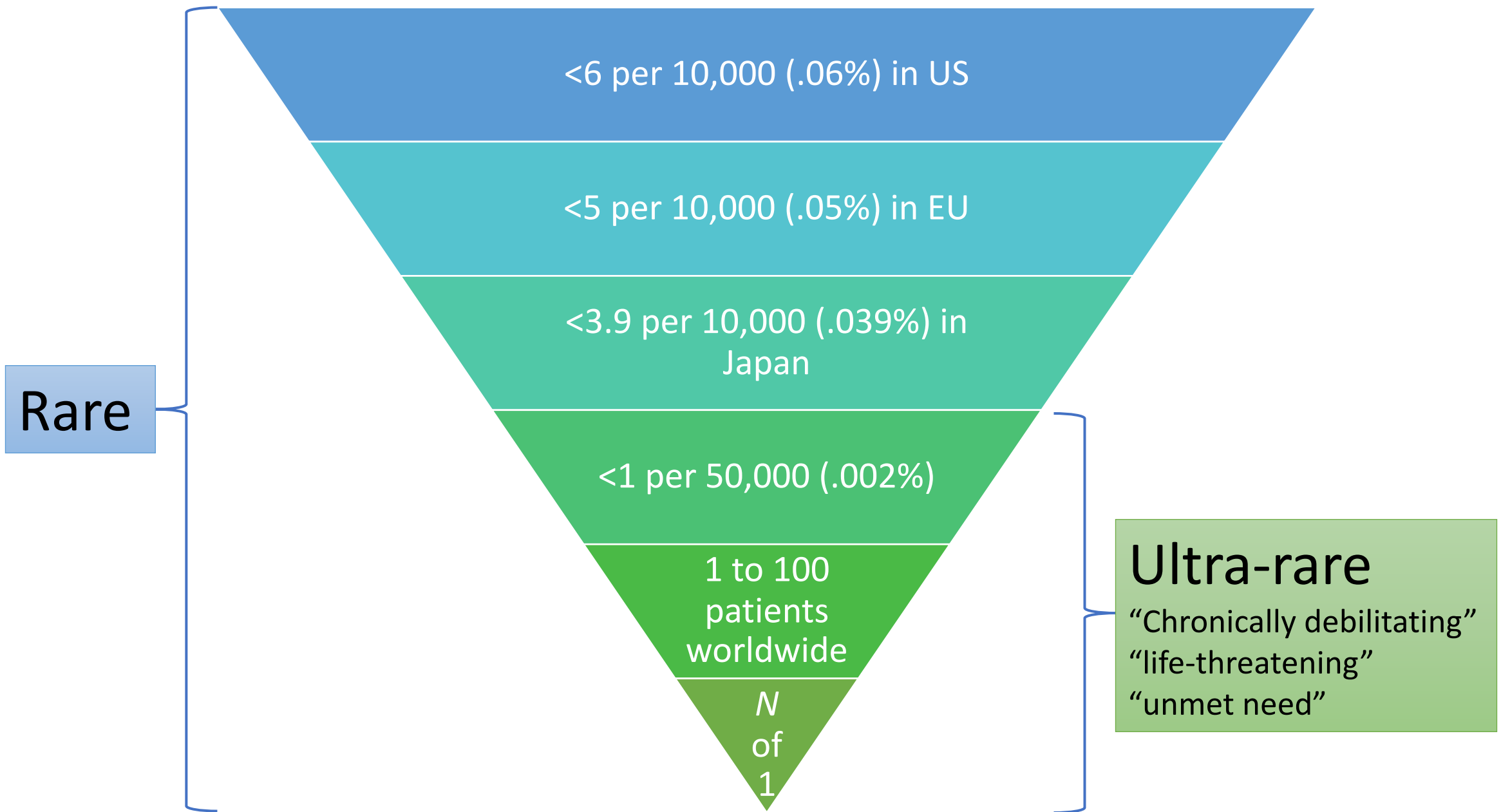
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Disclaimer:

Although I am often asked about planning data submissions, I am not a Regulatory Professional. This presentation is based solely on my own experience. Data submission decisions are very complicated and require written FDA agreement.

Rare





Rare

Ultra-rare

“Chronically debilitating”
“life-threatening”
“unmet need”

A case study

The following slides describe a fictitious drug and ultra-rare disease.

Any similarity to an existing program is unintentional.



This is Carrie...

She is a data scientist, and she has been assigned to work on a clinical program for the approval of a drug to treat an ultra-rare disease. It is in Phase 2 development. We know of 85 diagnosed patients in the world.

The compound is XYZ...



... and treats ultra-rare neurological genetic disease DEF...



A unique opportunity...



XYZ IS USED IN THE TREATMENT
OF ANOTHER NEUROLOGICAL
DISEASE.



IT WAS DISCOVERED THAT A SMALL
SUBSET OF PATIENTS TREATED FOR THAT
NEUROLOGICAL DISEASE REALLY SUFFERED
FROM A DIFFERENT DISEASE ALTOGETHER,
DEF.

...  patients have been taking !



Carrie is on a cross-functional team to evaluate the use of Real World Data for their Phase 2 protocol



The Team is tasked with identifying:

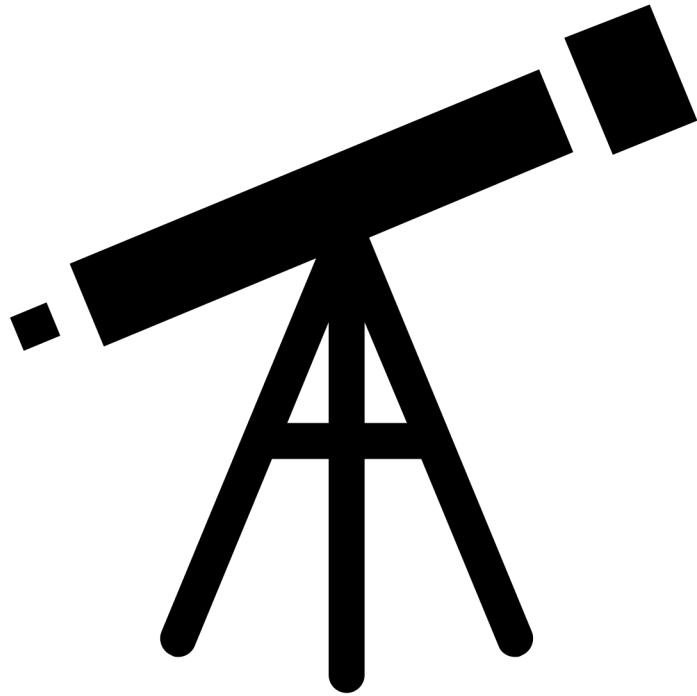
- Data sources that are fit for purpose
- Data collection methods that meet FDA regulatory requirements (e.g., study monitoring)
- Trial design that provides adequate scientific evidence to support the use of  in .



SOURCES OF REAL WORLD DATA

- Electronic health records (EHRs)
- Medical Charts
- Expanded Access Protocol Databases
- Disease registries
- Publications
- Public Records
- Insurance billing and claims
- Biometric monitoring devices (phones or watches)





In Ultra Rare Studies Every Bit of Data Counts

With only 85  patients, Carrie and her team will need to investigate all the data out there.

Types of Data Exchange Between Electronic Health Records (EHR) and Electronic Data Capture (EDC)



Noninteroperable

- No capability of electronic exchange of data
- Manual transcription of data elements like traditional EDC
- Possibility of transcription error

Interoperable

- Capable of electronic transmission of relevant data
- Automatically populate EDC fields
- May reduce transcription error
- Potential to unblind treatment allocation

Integrated

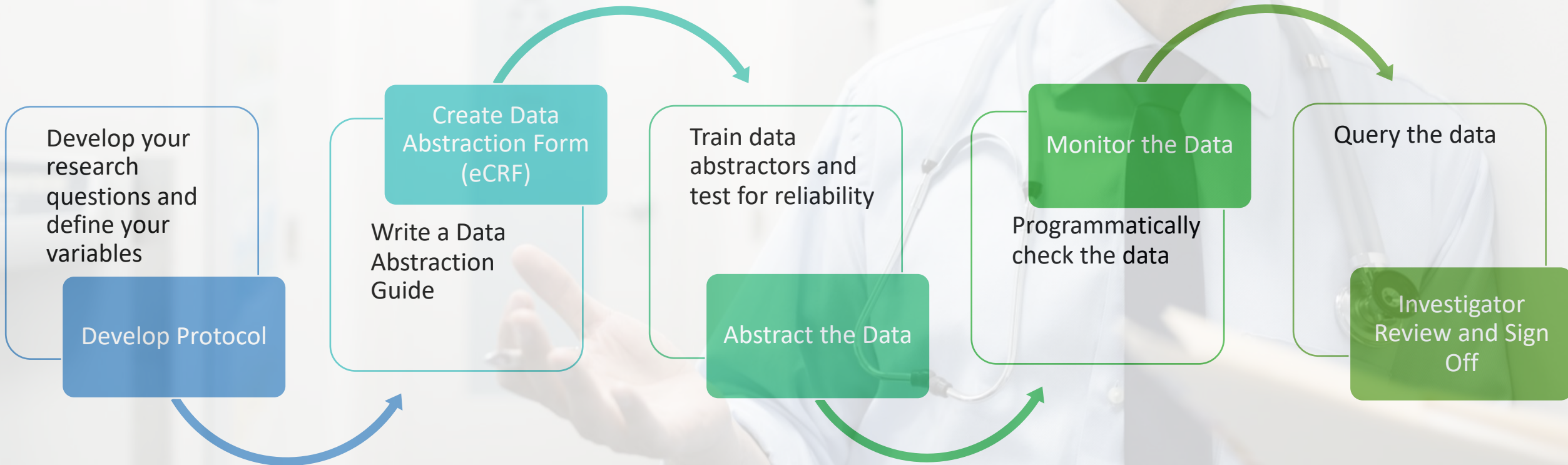
- Same as Interoperable
- Custom built research modules for entering trial data
- Fit for purpose

EHR Rules to Live By



- ✓ Informed Consent should cover all parties that may have access to protected health information.
- ✓ Stick to exchange of structured data (demographics, vitals, labs).
- ✓ Leverage data standards.
- ✓ Validate the exchange using SOPs, SDLC, Change Control, Quality Management Plan, Data Management Plan.
- ✓ Data sharing agreements.
- ✓ Investigator responsible for any data review, modification and sign off.
- ✓ Access Control and Audit Trails.
- ✓ EHR must retain author of the record for traceability.
- ✓ Electronic signatures for EDC records are subject to 21 CFR 11.
- ✓ FDA access to records for inspection purposes.
- ✓ Is the EHR certified by the Office of the National Coordinator for Health Information Technology (ONC) at the HHS?

Medical Charts



Medical Chart Extraction Rules to Live By

- ✓ Informed Consent should cover all parties that may have access to protected health information (PHI).
- ✓ Keep it from being a fishing expedition, prospectively define your variables.
- ✓ Utilize an Electronic Data Capture (EDC) developed with the same rigor and 21 CFR 11 compliance as traditional studies.
- ✓ Develop your abstraction form as if it is a Case Report Form (eCRF).
- ✓ Know your terms – develop a glossary of definitions of the variables for the Data Abstraction Guide.
- ✓ Train your data abstractors and complete sample extractions and verify.
- ✓ Monitor the data.
- ✓ Data abstractors should be blind to the objective of the study to reduce reviewer bias.
- ✓ Evaluate reliability in abstraction and address inter-rater (between different abstractors) or intra-rater (within the same abstractor) reliability.
- ✓ Prior to abstraction, develop a plan to identify patterns of missing data and how to handle missing data in the analysis.

Expanded Access Programs (EAP)

Expanded access or compassionate use is a way patients with a life-threatening or serious condition can receive treatment outside of clinical trials when there is no other alternative.

Patient:

- Signs Informed Consent

Physician:

- With Sponsor writes the protocol and gets FDA & IRB approval
- Oversees treatment
- Provides data to Sponsor

Sponsor:

- With Physician writes the protocol and gets FDA & IRB approval
- Provides drug
- Reports safety info to FDA

FDA:

- Reviews the EAP protocol
- Approves or declines protocol
- Receives Safety Reports

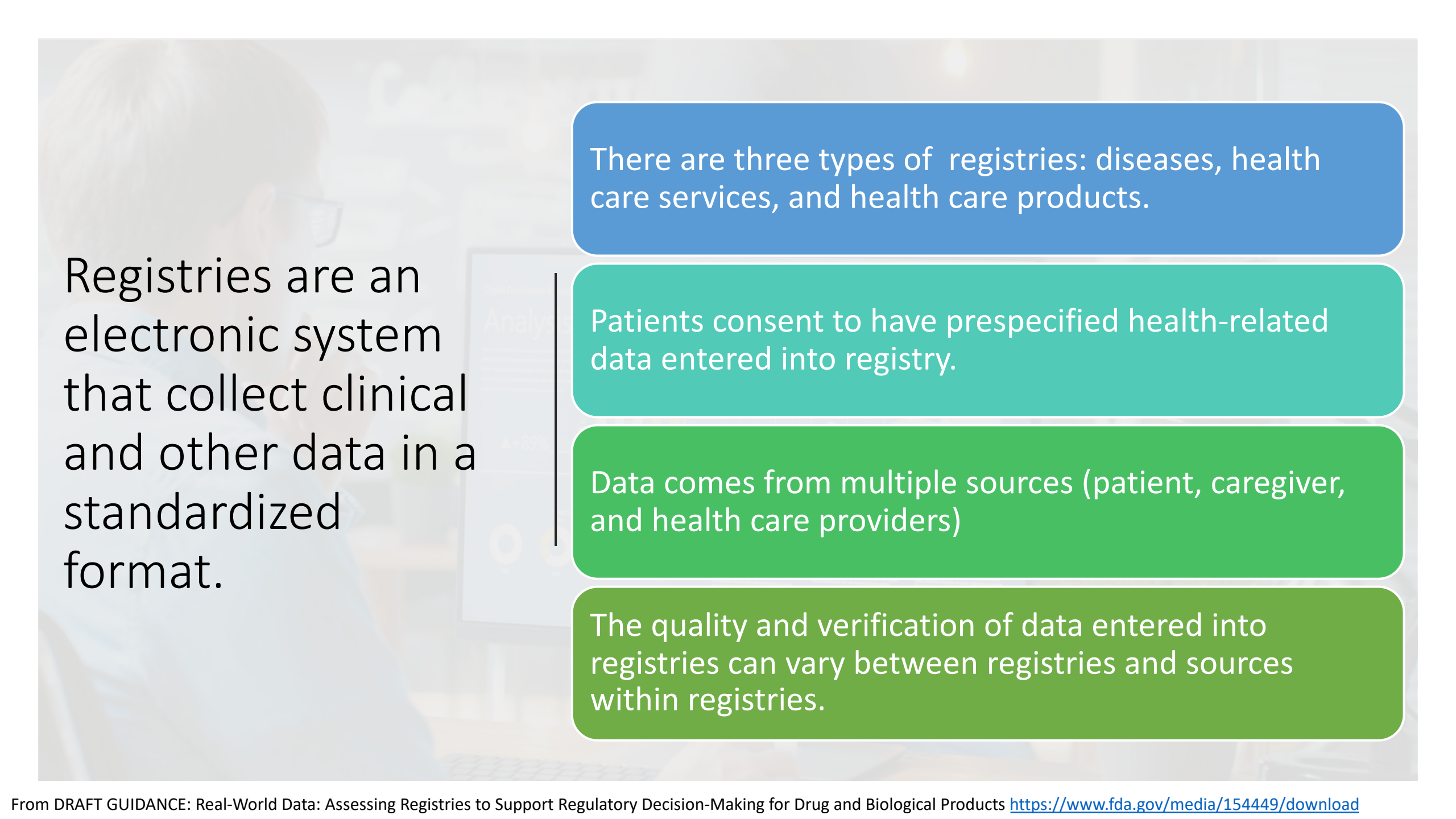
IRB:

- Reviews the EAP protocol
- Ensures patient consented to experimental treatment
- Approves patient access to drug



EAP Rules to Live By

- ✓ When establishing an EAP, a sponsor should include what data will be collected for the patient. This could often include information that is typically collected in a clinical trial with demographic, baseline and disease characteristics, safety, and efficacy data.
- ✓ The consent to participate in the EAP should include consent to share data, including with medical authorities such as the FDA.
- ✓ Extraction of data from the EAP can be done in a similar way to EHRs and Medical Charts.
- ✓ There are organizations that facilitate EAPs and will often have data forms collected on a regular basis from the Physician and sometimes the data is entered into a database.



Registries are an electronic system that collect clinical and other data in a standardized format.

There are three types of registries: diseases, health care services, and health care products.

Patients consent to have prespecified health-related data entered into registry.

Data comes from multiple sources (patient, caregiver, and health care providers)

The quality and verification of data entered into registries can vary between registries and sources within registries.

Registry Rules to Live By

- ✓ Is there sufficient informed consent and protection of PHI.
- ✓ Patients that have more severe disease may be more likely to be in a registry, or there may be other reasons why the patients may not be representative of the whole population, thus introducing bias.
- ✓ Potential data heterogeneity issues concerning variable approaches to data quality and lack of standardized collection.
- ✓ Consider if the data in the registry is fit for purpose in relevance, does it contain the data values we need?
- ✓ Is the data reliable in terms of data accuracy, completeness, provenance (audit trail), and traceability.
- ✓ Are the source records available for inspection by FDA?



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- Journal articles
 - Review articles
 - Case studies



Published Data Rules to Live By

- ✓ The confidentiality of human subjects and addressing PHI needs to be addressed via informed consent and sometimes a waiver from an IRB will be necessary in the event that informed consent is not possible (the patient has died).
- ✓ Published patient data may be biased toward reporting patients with severe disease or a remarkable outcome. They may not have patients from the full spectrum of disease.
- ✓ Bias can also be introduced based on the selection of dates to start collecting data and cutoff.
- ✓ Protocol should be developed before start of study with clear inclusion/exclusion criteria, what data will be collected and how, and the plan for analysis.
- ✓ Data should be collected with the same rigor as prospective clinical trials. Extraction of data should be in line with the suggestions for Medical Charts.
- ✓ Published data may help identify patients for inclusion in data extraction from medical charts or EHR.

Public Records

Organizations exist that act like private investigators that go out and search public records to determine the current contact information for a lost to follow-up patient or vital status. The work with EDCs or provide external data to CROs and sponsors.



Carrie found a lot of data... Is there a purpose for it?

Identify Patients:

1. EAP Database
2. Disease Registry
3. Case Studies
4. Review Articles
5. Partner Clinical Trial Data

Efficacy Outcomes:

1. EHR and Medical Charts
2. EAP Database
3. Partner Clinical Trial Data
4. Disease Registries
5. Publications
6. Public Records (Vital Status)



Describe Natural Course:

1. Disease Registries
2. Publications
3. EHR & Medical Charts

Safety:

1. EAP Database
2. EHR & Medical Charts
3. Partner Clinical Trial Data
4. Partner Safety Database

External Control Group:

1. Publications
2. EHR & Medical Charts
3. Partner Clinical Trial Data



Is the data “fit
for purpose”?

What is 'fit for purpose'?

Real World Data is of sufficient quality to provide Real World Evidence

“A ‘fit-for-use’ perspective applied to **data quality** assessments means understanding whether the data is appropriate to be used for its intended purpose to either attain knowledge, make decisions, or plan for the future.”

-Ngo, et. al.

FDA Definitions

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

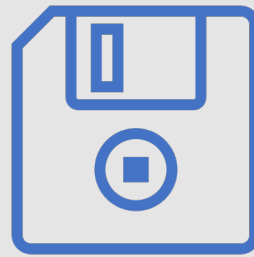
Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

How do you know your data is 'fit for purpose'?

Assess your Data using Data Quality Principles

Data quality principle	Sample DQ checks (adapted from Razzaghi, et. al.)
Numeric outlier detection	Plot continuous variables to identify outliers.
Temporal outlier detection	Create time trend graphs to detect gain or loss of motor milestones not typical of normal development or progression of disease.
Completeness of Records	Create metrics for patients for whom complete vital status data are available: date of birth, data of disease onset, date of death or last contact and perform cluster analysis by data source.
Concordance of facts	Create Venn Diagram of diagnoses, vital status and motor functions to understand how different definitions alter the overlap of the data sources to define disease course.
Plausible distribution of facts	Proportion of patients with invasive ventilatory support and visit to the ICU in disease cohort vs a cohort of healthy patients

Robust Data Collection Method



EDC System

(using Data Extractors)

- EHR (Noninteroperable)
- Medical Charts
- Publication Text

Electronic Data Transfer

(to EDC or tabulation data)

- Partner Clinical Trial Data
- EHR (Interoperable or Integrated)
- EAP
- Disease Registries
- Publication Data Supplements
- Public Records

Data security and integrity will be bolstered by choosing traditional and well accepted systems and processes.

Data Collection Rules to Live By

- ✓ Stick with your prespecified plans to avoid even the appearance of bias
- ✓ Define your data variables and stick to the definition – don't enter divergent data into the same variable.
- ✓ Ensure you have informed consent before collecting any data
- ✓ Protect Protected Health Information
- ✓ Maintain source traceability in data and meta-data
- ✓ Evaluate for duplicate data and integrate as needed
- ✓ Develop and utilize data monitoring practices
- ✓ Will need a creative but robust query process
- ✓ Avoid entering and reading in data from uncontrolled spreadsheets

Trial design that provides adequate scientific evidence

Ultra Rare
Is not
Typical

- Needs to show substantial evidence
- Adequate Well Controlled Studies (note the plural)
- Effect must be clinically meaningful
- Study report needs to contain sufficient detail of design, conduct, and analysis to support claim of substantial evidence
- Needs a valid control group (the drug effect is not from spontaneous change, placebo effect or biased observation)

Substantial evidence bar must be met regardless of rarity; it is what qualifies as substantial evidence where flexibility may be exercised.



Carrie's Team has proposed two Trial Designs

Study Objectives:

1. An Observational Study with a Non-concurrent External Placebo Control - *Utilizing placebo efficacy data from previous  studies conducted by the company's partner*
2. An Observational Study with Untreated Natural History External Control

The study design for , particularly if it is meant as a pivotal study, will require FDA feedback. FDA may reject the proposal or may require the company to complete a randomized controlled trial to verify clinical benefit.



To describe the safety, tolerability, and efficacy of  in patients with 

To describe the natural disease course of  from symptom onset to initiation of treatment or death

Key Takeaways

1. Real World Data has to be of high quality, 'fit for purpose' and show meaningful clinical effect to be considered Real World Evidence.
2. Collecting Real World Data for submission comes with challenges of traceability, integrity, and effort to reduce bias is needed.
3. It is difficult to power an ultra rare disease study, but because of the Orphan Act, sponsors can think outside of the box to establish substantial evidence.



Look up my presentation from EU Connect 2021
“Hey Data Scientist: Are You Following the Rules
and Your Conscience?”

See how Charles learned how
to do the right thing with real
world data



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