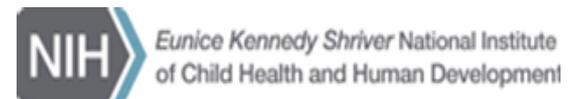


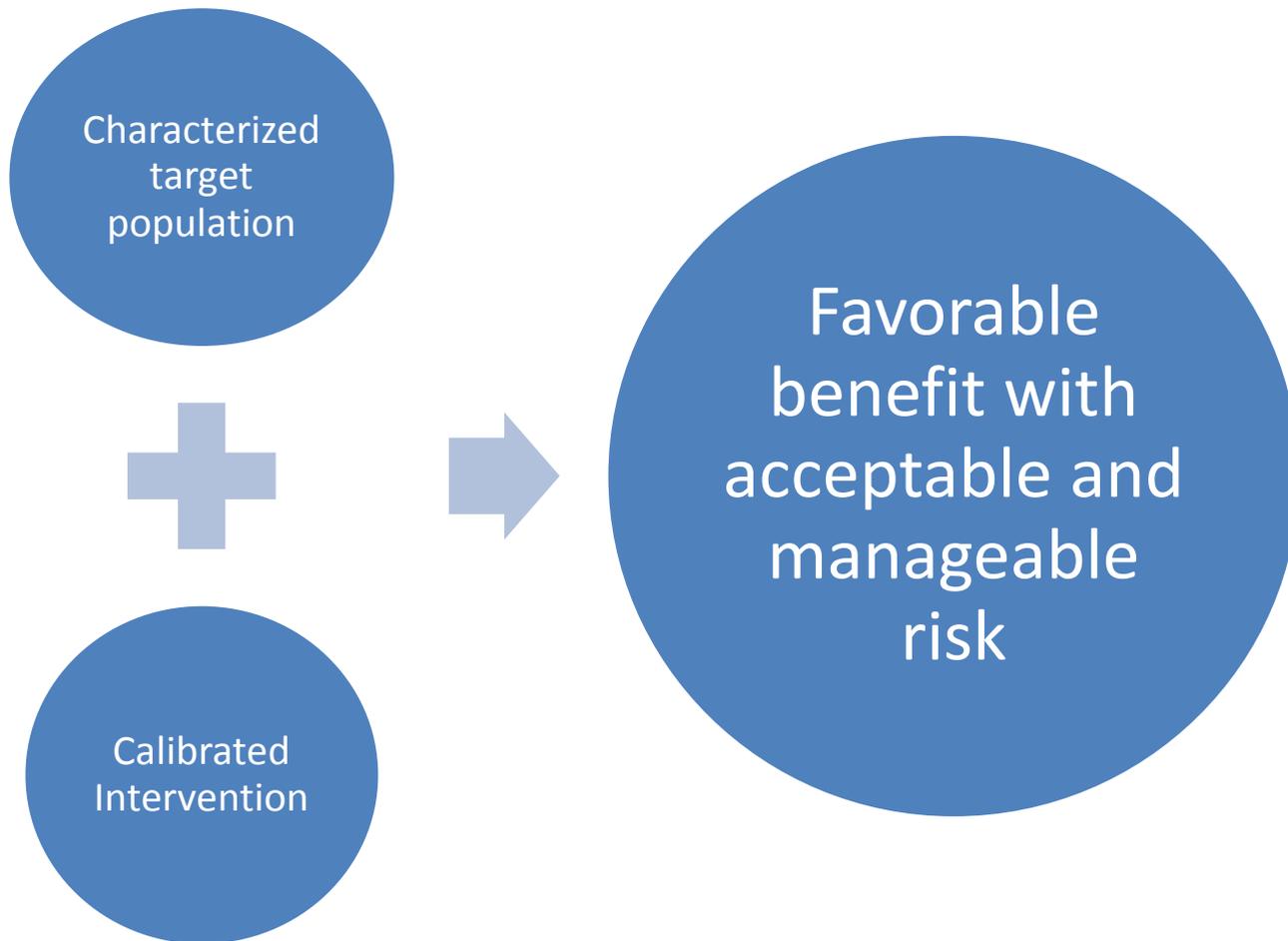
# Clinical Trial Design Process: An Introduction

Steven Hirschfeld, MD PhD  
Captain, USPHS

Associate Director for Clinical Research  
*Eunice Kennedy Shriver* National Institute of Child  
Health and Human Development



The End Result- People receive interventions calibrated to provide the most favorable benefit to risk



# Approaching the Topic

- This presentation will have three parts
  - Establishing a Framework- what are the characteristics of a system that can provide the data and experience to make decisions
  - Operationalizing the activity- considerations of the activities that need to be addressed and integrated
  - Analyzing the outcomes and making decisions- several interim decisions may arise before deciding on the end result

# Studies are contrived situations

- A study is designed in order to minimize bias and uncertainty
- A study is contrived and is meant to model circumstances that are generally complex
- The model is intended to be generalized to people similar to those that participated in the study and perhaps extended to other circumstances
- A study should be designed by intent so that the outcome can be replicated

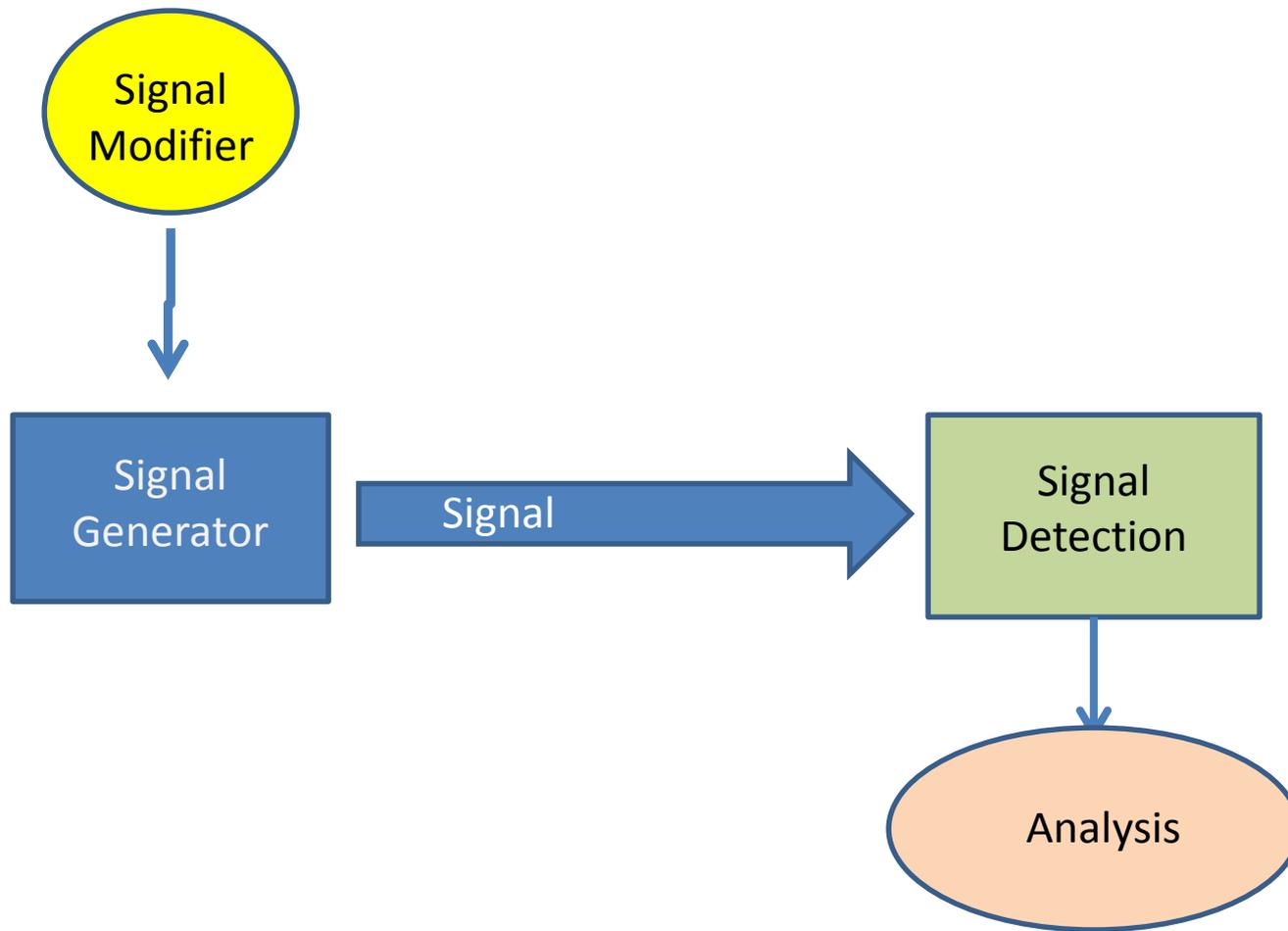
# Clinical Trials

- Clinical trials are one example of a contrived situation to learn about
  - An intervention
  - A population
  - A condition
- Several definitions exist for what is a clinical trial with the common theme that a person is exposed to an intervention based on a prospective protocol or plan with a primary objective to evaluate the intervention

# How do we get to the intended end result?

- The reality is that we may not know in advance for any individual, but we can project what is likely to occur in a population of interest based on prior data and experience
- The prior data and experience come from various sources- some from studies in a structured laboratory setting and some from studies in a structured clinical setting

# Basic Generic Experimental Design



# Signal Characteristics

- Discrete or continuous
- Amplitude and phase (direction)
- Frequency and jitter (frequency variability)
- Pattern
- Uniqueness = signature
- Signal characteristics should be distinguished from noise characteristics

# Signal Detector Characteristics

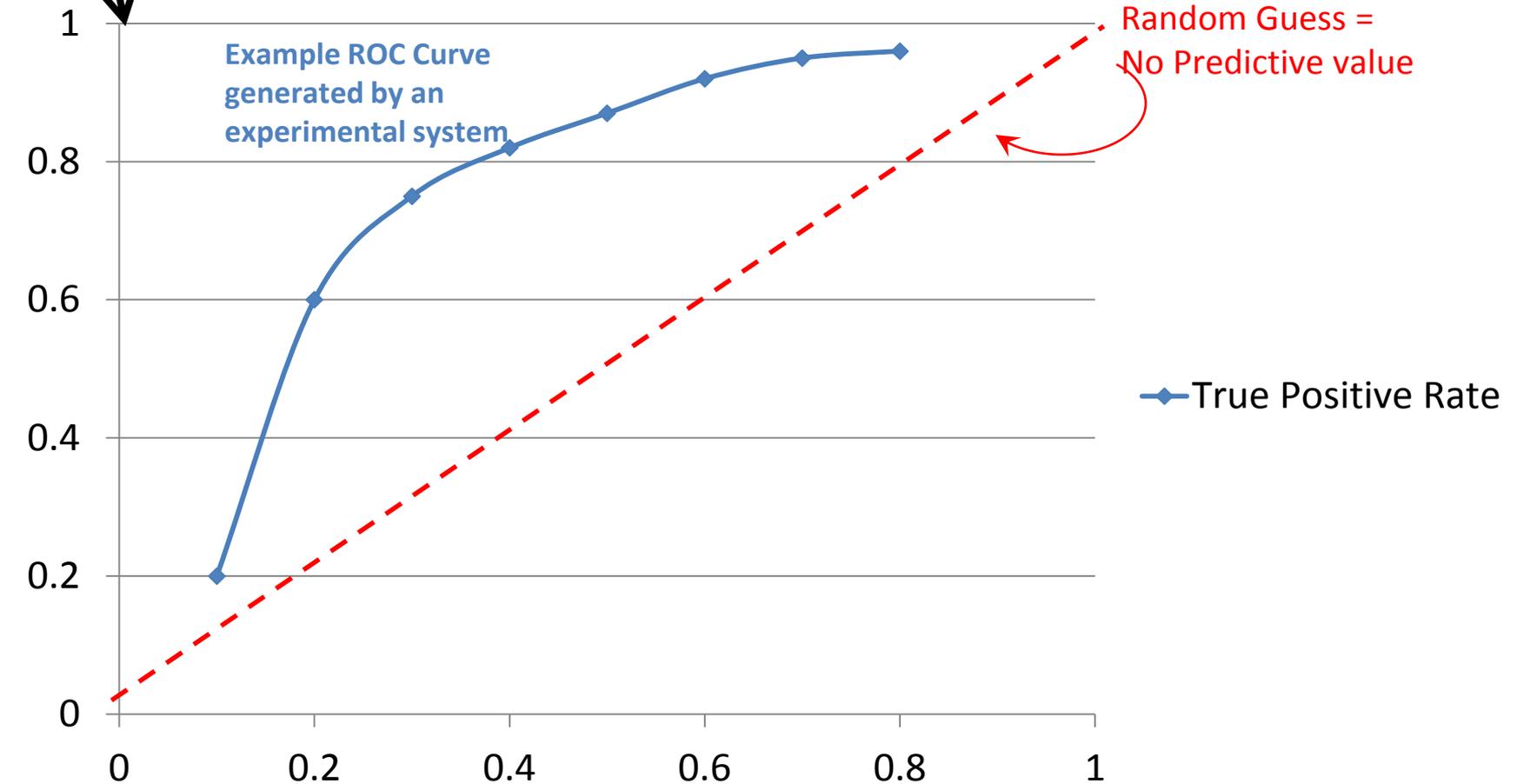
- Detector discrimination
  - Sensitivity=  $\text{true positives}/(\text{true positives} + \text{false negatives})$
  - Specificity=  $\text{true negatives}/(\text{true negatives} + \text{false positives})$
  - Positive likelihood ratio=  $\text{sensitivity}/(1-\text{specificity})$can distinguish signal from noise
- Detector read out is objective, consistent (not operator dependent), and ideally quantifiable for analysis

# Receiver Operator Characteristic (ROC) Curve

- First developed in 1940s to characterize radar signals to distinguish objects
- Displays how a system performs as the discrimination threshold is changed
- Plot of true positive rate versus false positive rate as a function of changing threshold settings (sensitivity versus 1-specificity)
- Ideal performance is maximal detection at minimal signal (fewest false positives)
- Area under the curve is maximized as system is optimized
- Primarily applicable to binary outputs- yes or no, there or not there, above threshold or not

# Example of ROC Curve

Ideal Predictive value ↓



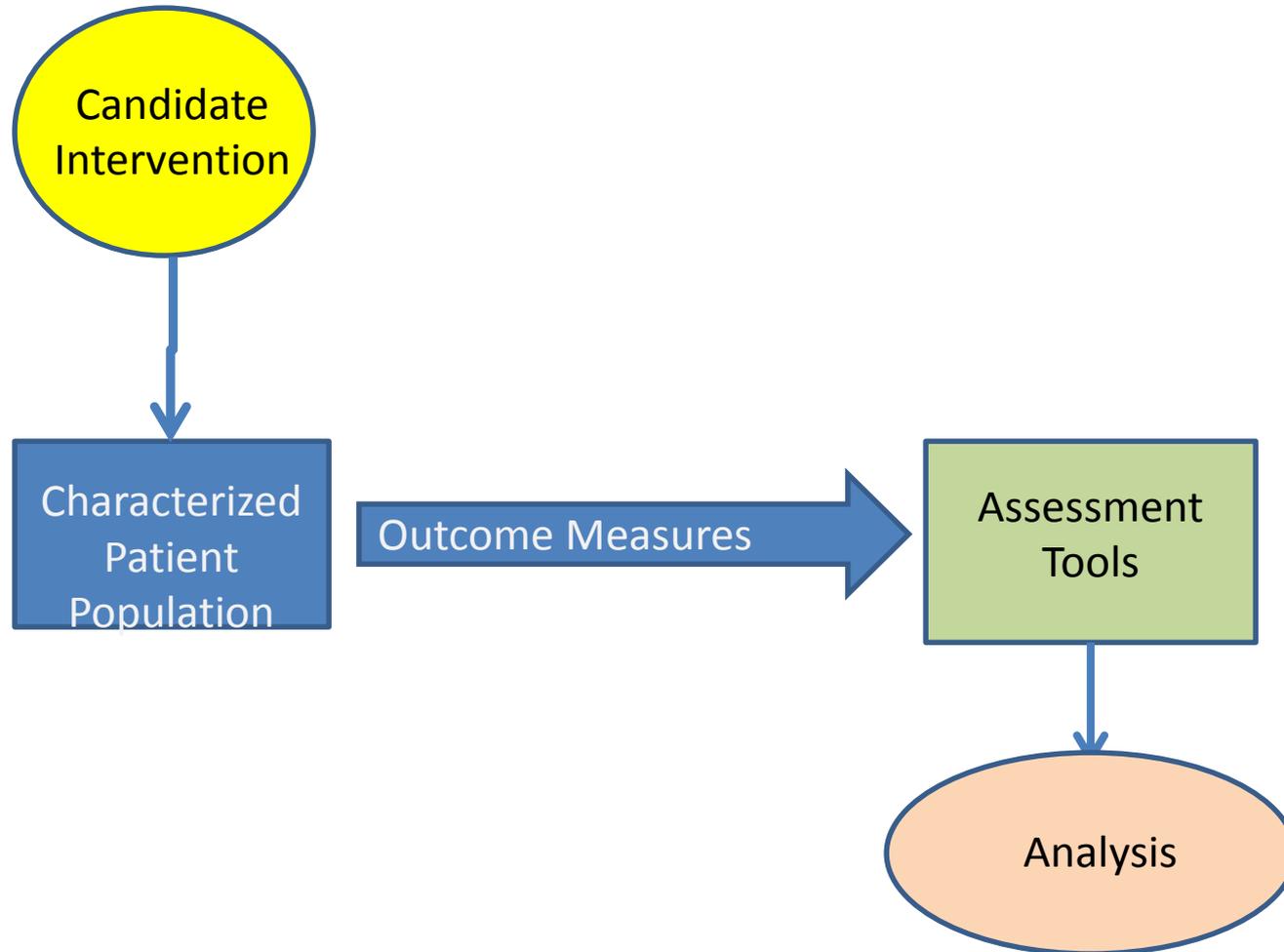
# System Optimization-1

- Signal generator produces relevant signal(s) with detectable characteristics
- Signal(s) contain(s) relevant information
- Signal detector with sufficient
  - Sensitivity=  $\text{true positives}/(\text{true positives} + \text{false negatives})$
  - Specificity=  $\text{true negatives}/(\text{true negatives} + \text{false positives})$
  - Positive likelihood ratio=  $\text{sensitivity}/(1-\text{specificity})$
  - ROC Curve = plot of threshold changes in  $\text{sensitivity}/(1-\text{specificity})$   
to distinguish signal from noise
- Signal modifier modulate(s) relevant signal(s)

# System Optimization-2

- Demonstrate and document the parameters that support system optimization
- Provide the sensitivity, specificity, positive likelihood ratio, and ROC Curve for the signal detection system to indicate the system optimization
- Provide all of the specific signal data for the signal modifier on the optimized system
- Describe the relationship between signal modifier changes and signal detection changes

# Basic Experimental Design for a clinical trial



# Model Application to Clinical Trials

- Signal Generator = participant population
- Signal = outcome measure(s)
- Signal detector = outcome measure(s)  
assessment tools
- Signal modifier = intervention
- Optimization = maximal benefit with  
acceptable risk
- Analysis = generalizable information

# Clinical Trial Rationale

- Generate data
  - That can only be addressed through enrolling human participants
  - Fill knowledge gaps
  - Can lead to generalizable knowledge as part of a larger information plan

# When is a study that applies an intervention not a clinical trial

- Studies not intended or designed to prospectively generate data to support generalizable knowledge are generally not considered clinical trials.
- Such studies could be considered quality improvement or decision support studies, depending upon characteristics and circumstances
- Such studies could also be unethical if they expose participants to risk without either the likelihood of direct benefit or generalizable information

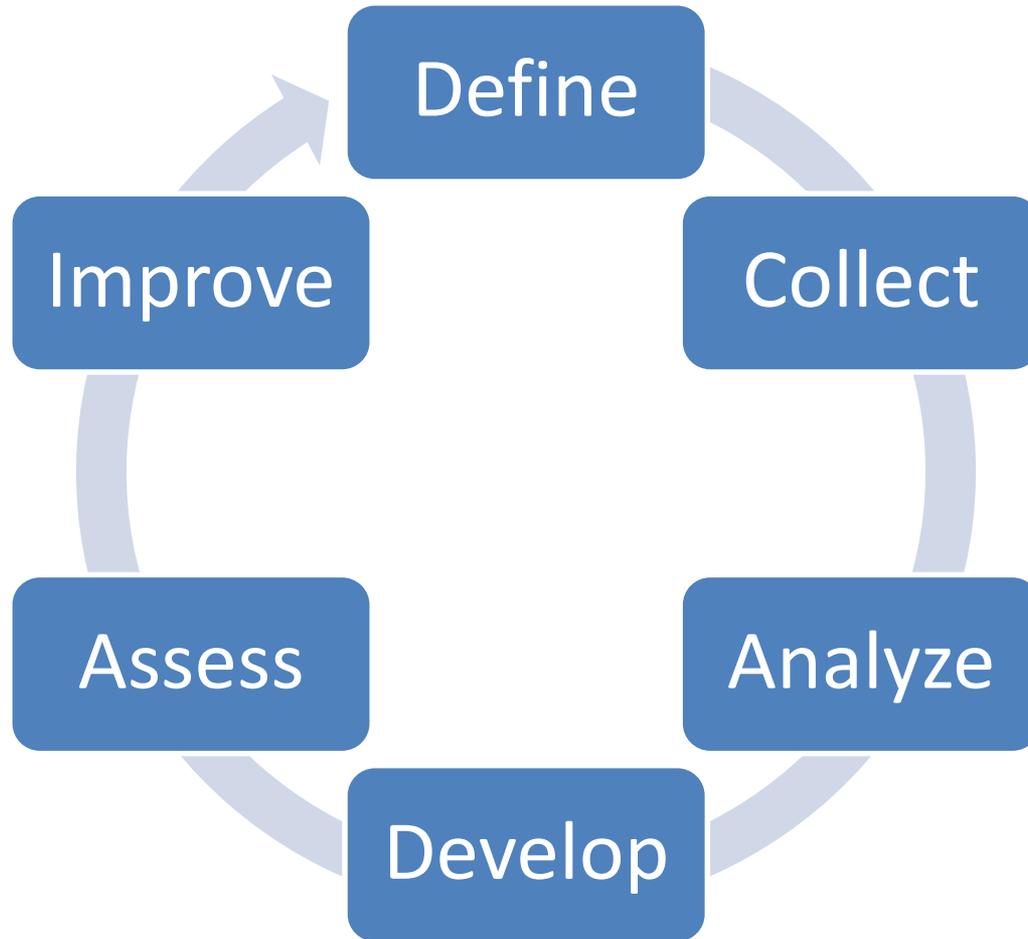
# Interim Summary

- Clinical trials are artificial or contrived constructs to provide data that is otherwise not available
- Clinical trials can be framed similarly to a generic signal detection system
- System optimization to maximize signal to noise and minimize bias and uncertainty can improve precision and analysis

# Clinical Trials in Context

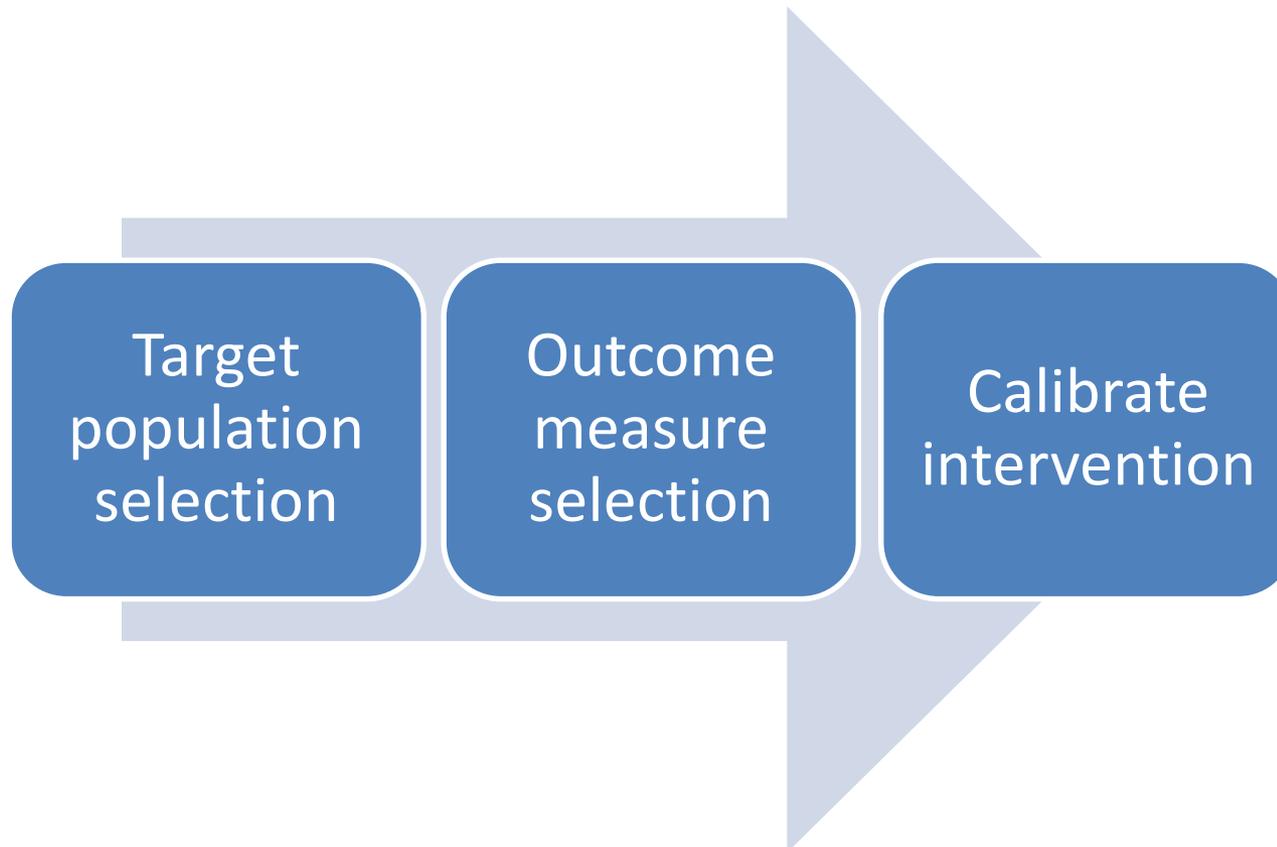
- A clinical trial is rarely performed as an isolated activity
- A clinical trial is typically planned and implemented as part of a larger project to learn more about a condition, a population, an intervention
- Each clinical trial will have specific objectives and outcomes but will also contribute to the larger knowledge bases about the intervention, the target population, the condition, and the general process of clinical trials

# Generic Design Process



# Development Sequence

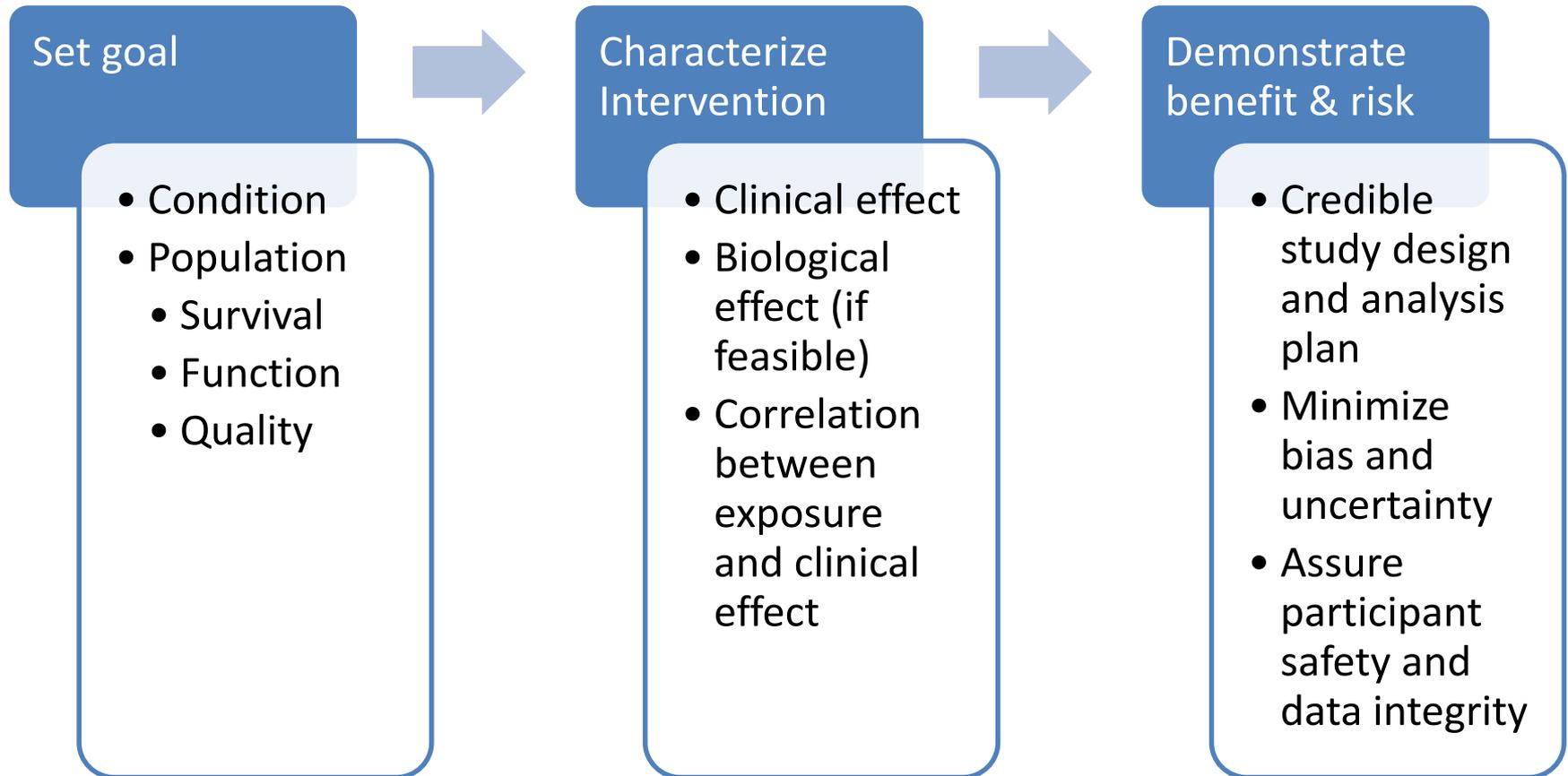
- While any empirically successful approach is plausible, a proposed approach is:



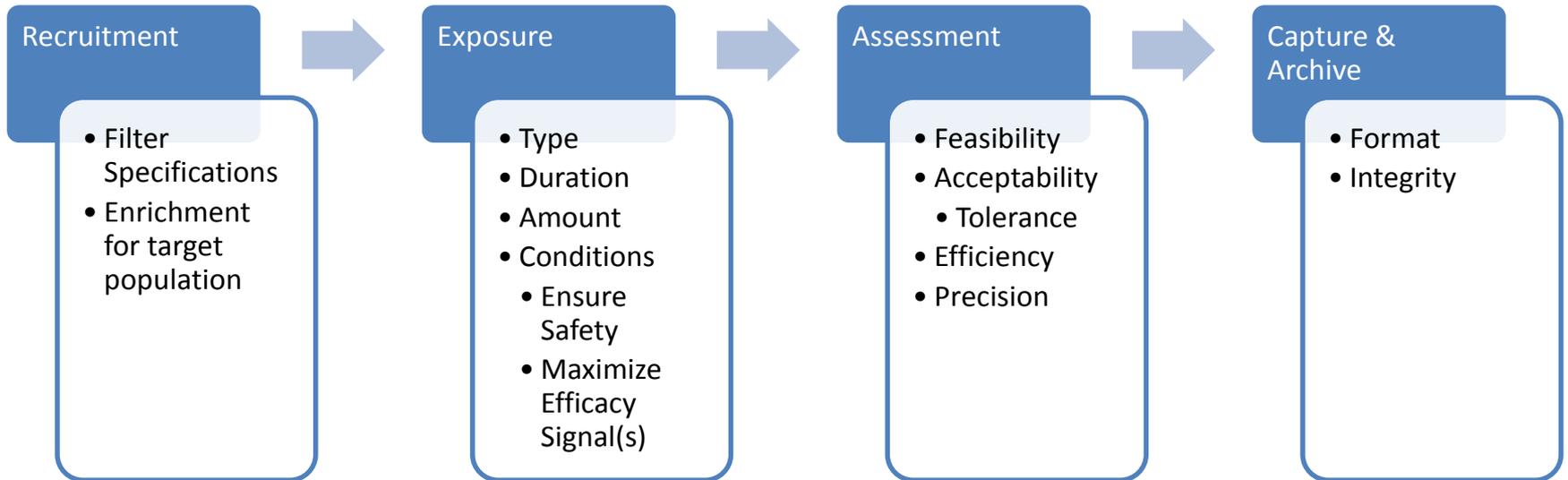
# Clinical Trial System Goals

- Select relevant *population*
- Select informative signals = *outcome measures*
- Optimize signal detection by *outcome measure assessment* selection and adjustment
- Calibrate signal modulation through adjustment of *intervention* exposure (dose, duration, concentration, intensity, etc.)

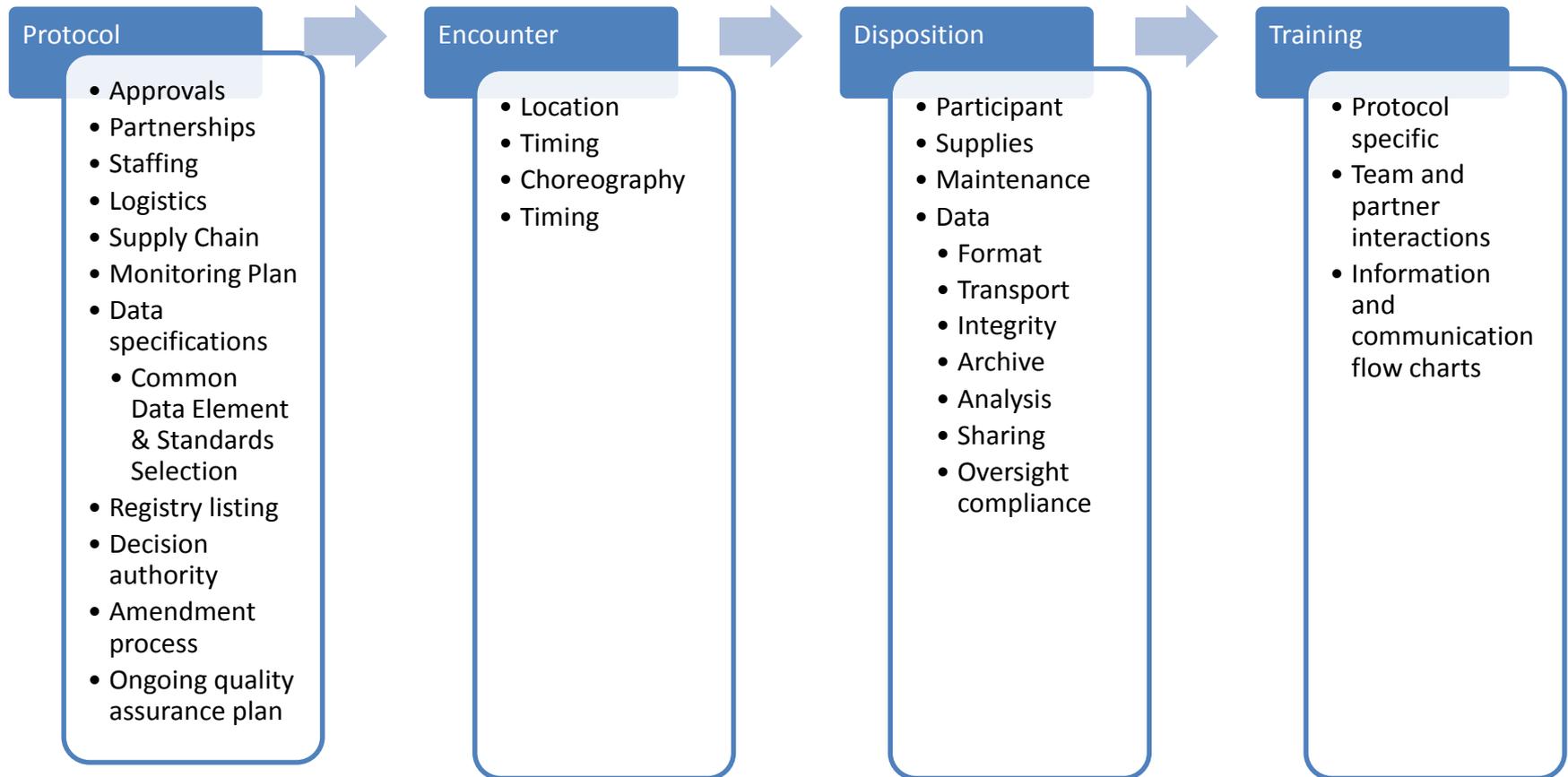
# Clinical Development Plan



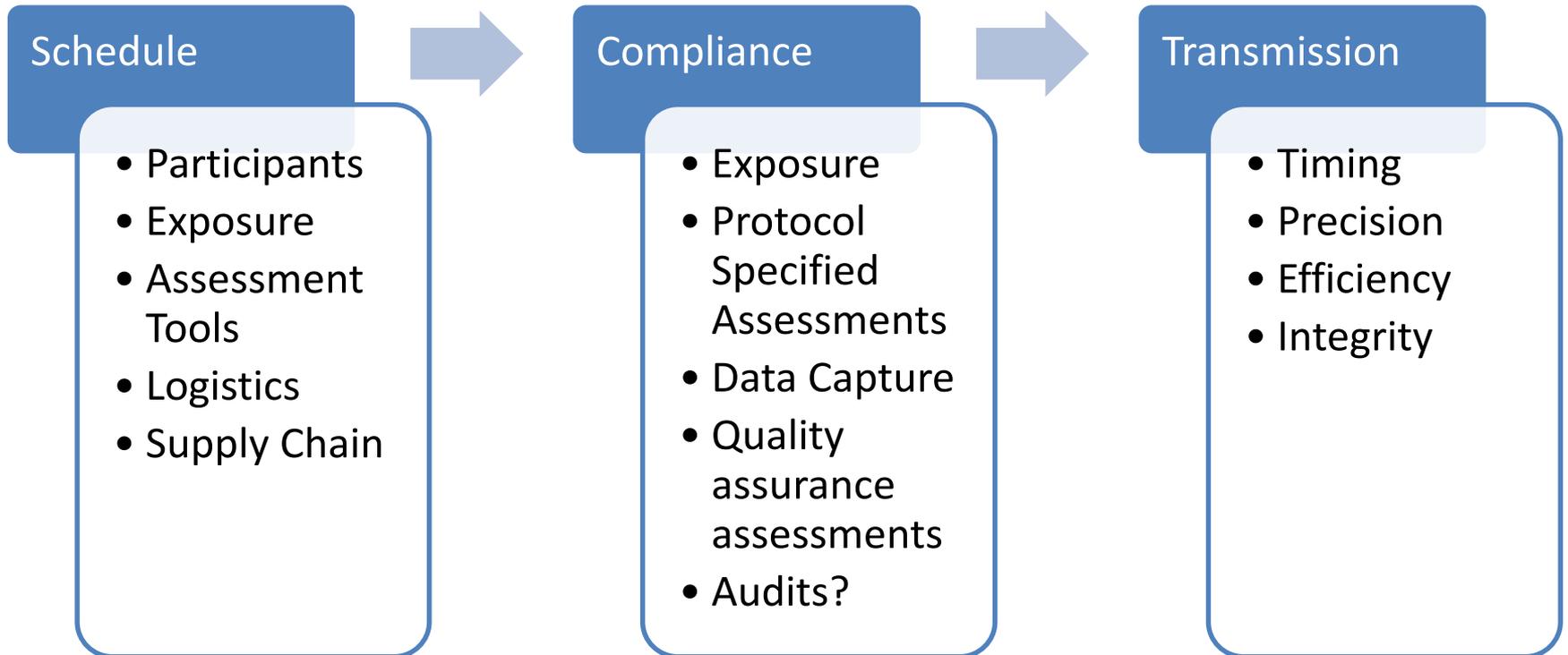
# Study Design



# Study Operationalization



# Study Implementation



# Data Analysis

- Data processing
- Analytic dataset production
- Protocol and statistical analytic plan specified analyses
- Exploratory analyses

# Communication

- Ongoing with communication flow charts
- Oversight compliance
  - Sponsor
  - Monitoring
  - Regulatory oversight
- Participant communication
- Results dissemination
- Registry updates

# Process Integration

- Planning and Project Management
- Construct layers and contact points between layers
  - Concept
  - Planning
  - Operationalization
  - Implementation
  - Analysis and sharing
  - Communicating individual, interim and analytic results
- Develop flowcharts and checklists
- Maintain flexibility

# Proof of Concept

- Validate target population
- Quantify clinical effect of exposure
- Decision
- Information enabling decision (input)
- Expected outcome(s) from the decision
- Actual outcome from the decision
- Adjust weights of drivers such as fast, cheap, and good

# Decision Support

- Each Milestone leads to a decision point
- To make the decision, data collection prior to the decision point must enable decision making.
- The enabling information must be identified in advance and collected during studies or from a reliable source
- The decision enabling information may not be the primary goal of a particular study, but must be included and carefully collected

# Enabling Information

- The decision enabling information should be identified through metadata tags and compiled into a repository to provide historical and collective information that can lead to a learning system
- The enabling information can be a source for decision modeling to improve efficiency and predictability