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Clinical Development for Medical Devices: Regulatory Role

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AHWP
Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICES HARMONIZATION IN ASIA

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Agenda

- Phases of Clinical Studies
- Clinical Evidence: Planning Process
- Determining Design of a Clinical Trial
- Examples of Clinical Evidence

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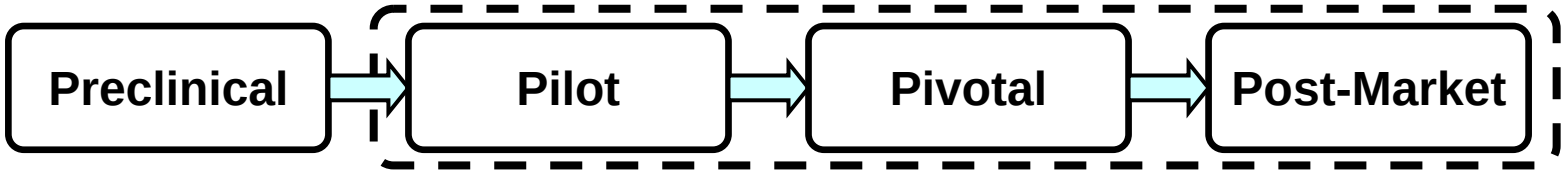
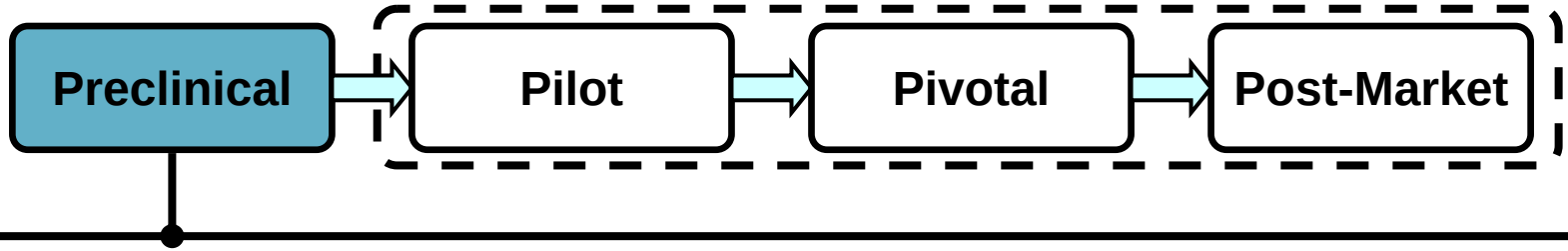
Phases of Clinical Studies



There are 4 phases in a clinical investigation:

1. *Preclinical*
2. *Pilot or Feasibility*
3. *Pivotal*
4. *Post-Market*

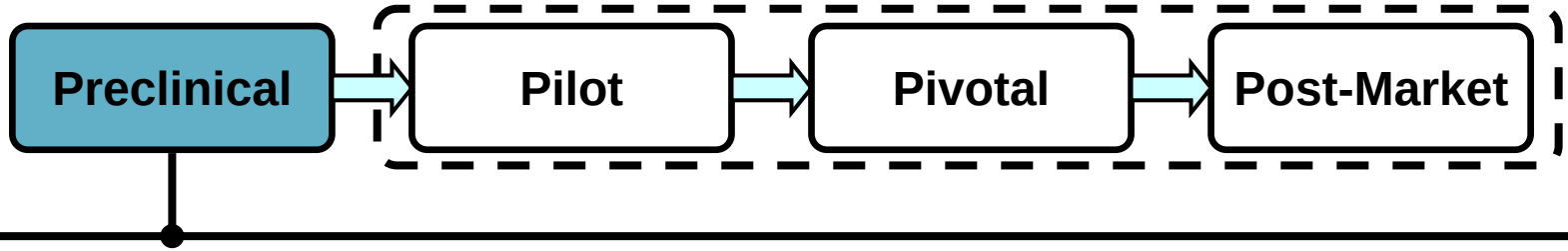
Phases of Clinical Studies



- The basic goals of preclinical investigations are:

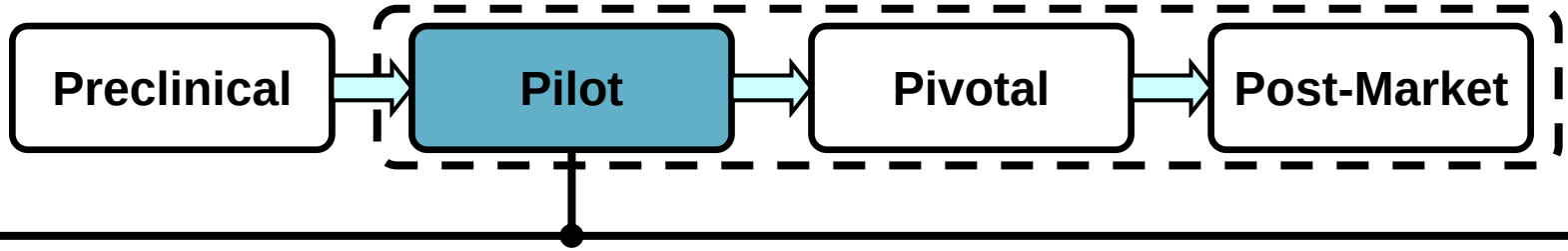
1) *Perform animal and lab tests to:*
   - Device performs the way it is supposed to
   - Determine if device will be safe for human trials
   - Assist in the design of a pilot trial
2) *Gather safety information to start clinical trials*
3) *Apply for Pre-market approval*

Overview of EU & FDA Clinical Regulations



- Study Design
  - *Preclinical Laboratory and Animal Studies*
    - 21CFR Good laboratory practice for non-clinical laboratory studies
  - *Development of a Clinical Trial Protocol*
    - 21CFR820.30 Quality system regulations: Design Controls
    - ISO 13485 Quality system for medical device manufacturers
    - ISO 14971 Medical devices- Application of risk management to medical devices
    - ISO 10993 Biocompatibility Series
  - *IRB Selection, Review, and Approval*
    - 21CFR56 Institutional Review Boards
  - *Formal Pre-Submission Meetings with the FDA*
    - §205 of the FDAMA: Pre-IDE Submission Meeting
    - §513(a)(3)(d) of the FDCA: Determination Meeting
    - §520(g)(7) of the FDCA: Agreement Meeting

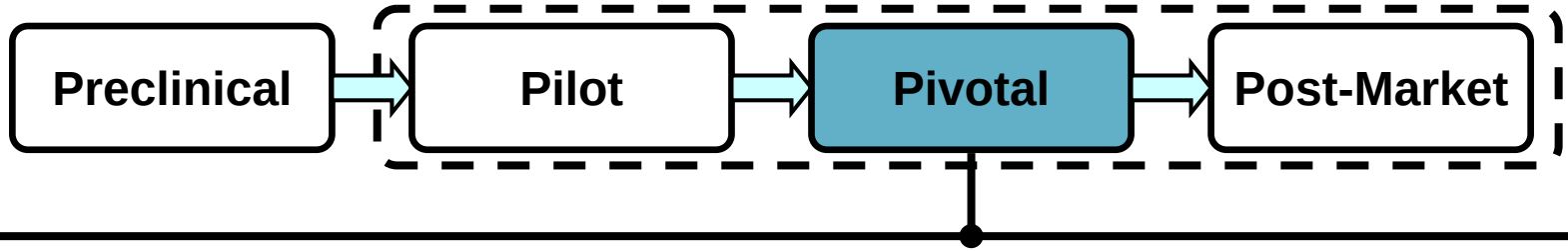
Phases of Clinical Studies



- The goals of pilot studies (also known as a feasibility study) are to:
  1) *Determine if first human use of device is safe*
  2) *To generate data and define patient groups*
  3) *Assist in the design of the pivotal trial*

- Pilot studies involve the initial application of the medical device to a small number (<100) of human patients from a few sites

Phases of Clinical Studies



- The primary goal of the pivotal study is to collect the data necessary to:
  1) *Determine if the device is performing as intended*
  2) *Determine if the device is safe and effective for human use*
  3) *Support market approval*
- Pivotal studies conducted after pilot studies
- Involve an expanded patient population (>1000) in multiple sites around the world
- Longer term studies-9 to 12 month primary endpoint, follow-up up to 5 years

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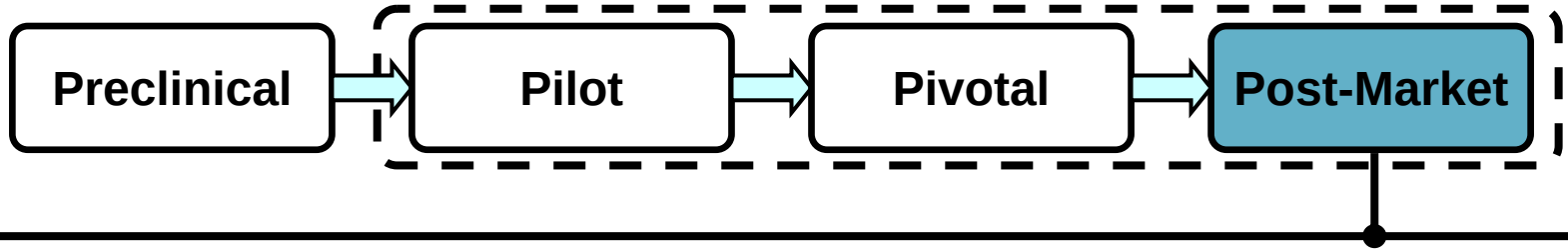
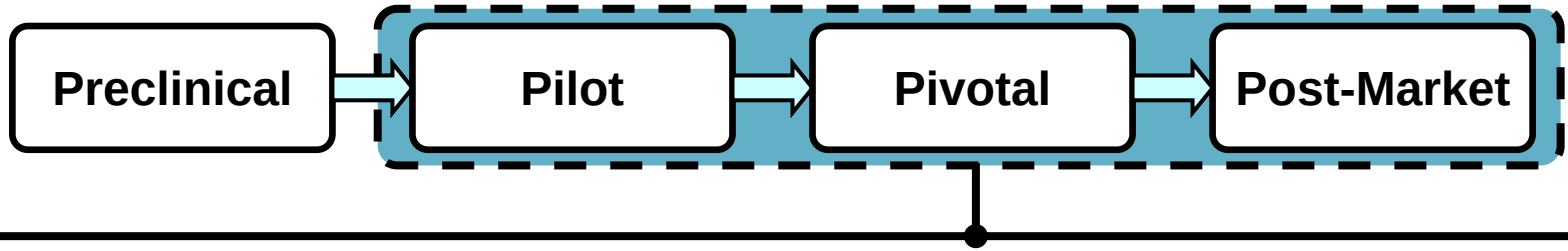
Phases of Clinical Studies



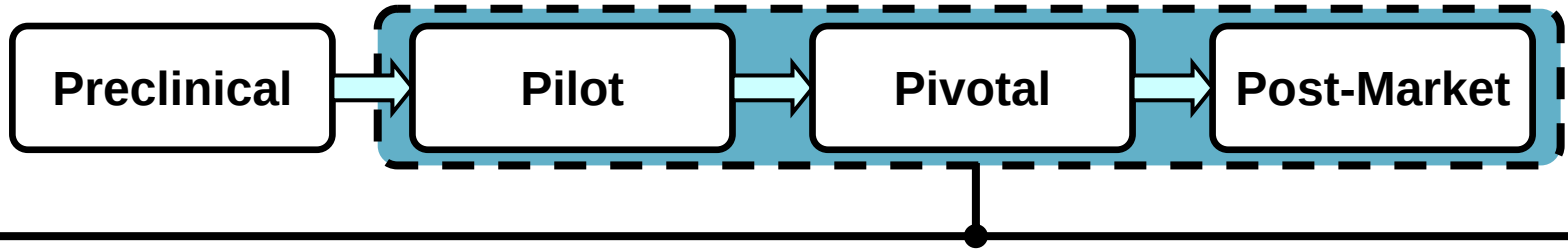
- Post-market studies are conducted to document "real-world" incidents to:
  1) *Determine if the device is performing as intended*
  2) *Determine if the device is safe for human use*
  3) *Identify new indications for the device and future improvements for the device*
- Post-market studies involve an expanded patient population (>1000) in multiple sites through additional clinical trials or registries global

Overview of EU & FDA Clinical Regulations



- Study Initiation
  - *Clinical Investigator Selection, Review, and Approval*
    - 21CFR812.43 Selecting investigators and monitors
    - 21CFR812 Subpart E – Responsibilities of investigators
    - 21CFR54 Financial disclosure by investigators
- Subject Enrollment
  - *Current Good Clinical Practices*
    - 21CFR812 Investigation device exemption
    - ISO14144 Clinical investigation of medical devices for human subjects
  - *Informed Consent and Protection of Subjects*
    - Declaration of Helsinki
    - 21CFR21 Protection of privacy
    - 21CFR50 Protection of human subjects

Overview of EU & FDA Clinical Regulations



- Conducting Clinical Investigations
  - *Data Collection and Management*
    - 21CFR11 Electronic records; electronic signatures
    - 21CFR56.115 IRB records
    - 21CFR81 Subpart G – Records and Reports
    - MEDDEV. 2.7.1 Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies
  - *Monitoring Studies*
    - 21CFR812.46: Monitoring investigations
  - *Adverse Event Reporting*
    - 21CFR822 Post-market surveillance
    - MEDDEV. 2.12-1 rev.5 Medical Devices Vigliance System
    - MEDDEV. 2.12-2 Post-Market Clinical Follow-Up
- Closing Study
  - *Final Study Report*
    - 21CFR54 Final disclosure by clinical investigators

Phases of Clinical Studies

Clinical Investigations
Clinical Studies

Clinical Investigations ARE NOT THE SAME AS Clinical Evidence

All mean the same & used interchangeably

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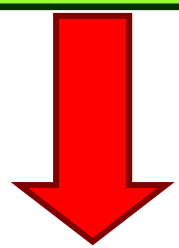
Phases of Clinical Studies

Routine Post Market Surveillance
Complaint Investigations
Literature Reviews
Vigilance Reports



These ARE NOT considered clinical trials
But are key components of Clinical Evidence

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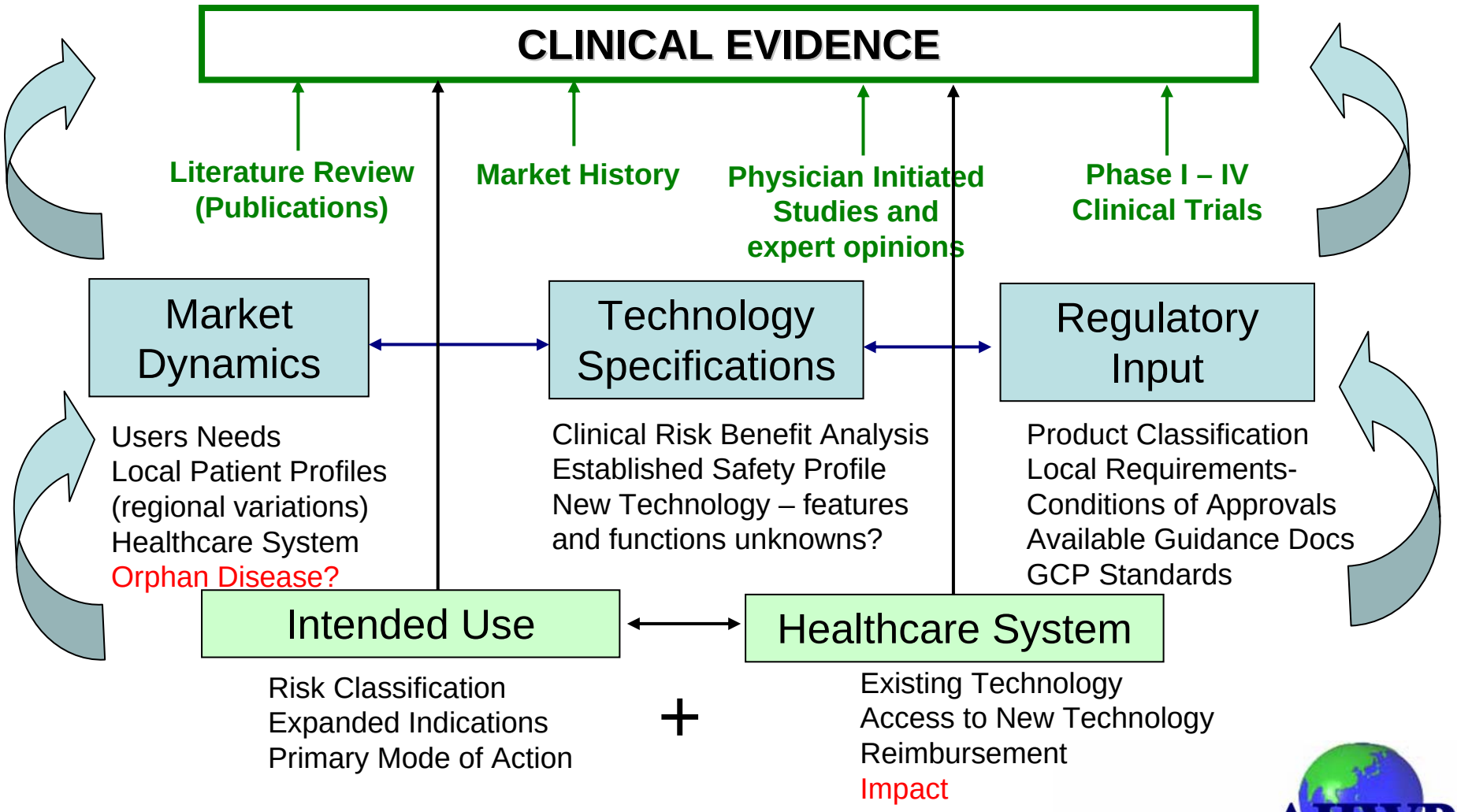
Clinical Evidence: The Planning Process



Clinical Evidence: The Planning Process

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CLINICAL INVESTIGATION

Literature Review (Publications) | **Market History** | **Physician Initiated Studies** | **Phase I – IV Clinical Trials**

Market Dynamics

Users Needs
Local Patient Profiles
Healthcare System
Orphan Diseases

Technology Specification

Clinical Risk Benefit Analysis
Established Safety Profile
Technology features
Human factors & workflows?

Regulatory Impact

Product classification
Local requirements
Available Evidence Docs
GCP Standards

CLINICAL EVIDENCE

Intended Use

Risk Classification
Expanded Indications

Healthcare System

Existing Technology
Access to New Technology
Reimbursement
Impact

ISO Standards, Bench Testing, Validations & Quality Systems

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Clinical Plan/Program Development

Important considerations when developing a clinical program:

Address safety, efficacy, and long-term performance concerns throughout the entire product lifecycle.

- *Preclinical data demonstrate initial product safety and performance to support human clinical studies*
- *Pre-market clinical data demonstrate initial product safety and efficacy to support market approval*
- *Post-market data demonstrate long-term product performance/effectiveness*

Ensure sufficient level of clinical evidence has been collected.

Confirm that clinical trials are well designed involving randomization, blinding, endpoints and a control group, for their pre-market and post market studies with long-term patient follow-up.

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Determining Design of a Clinical Trial

Questions to consider:

1. What type of study?
2. What type of patients?
3. What type of lesions?
4. What type of outcomes?

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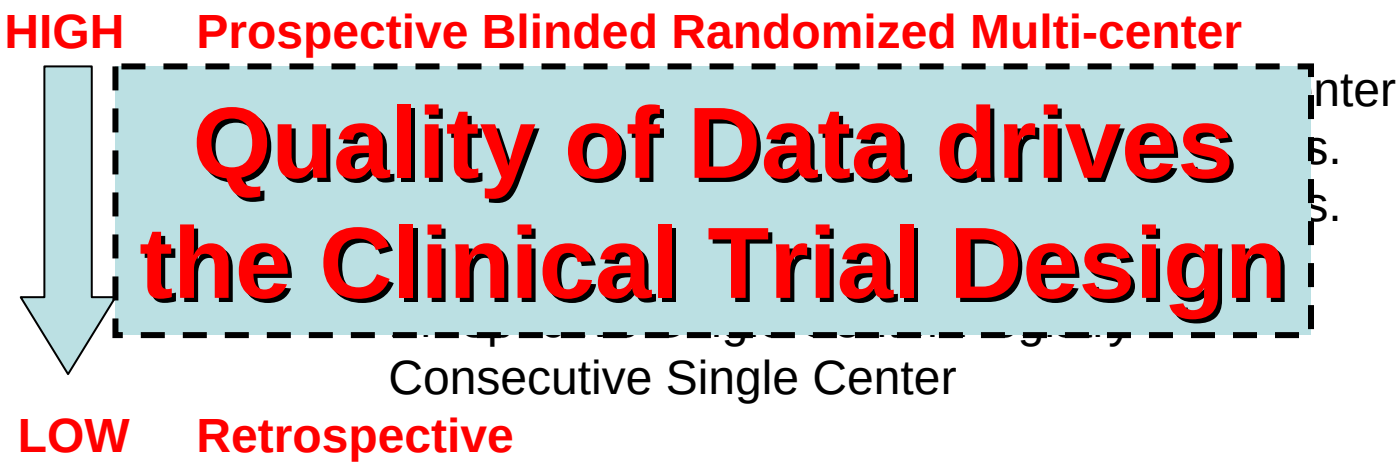
Determining Design of a Clinical Trial

1. What Type of Study?



Definition Key

Prospective = Starts in the present and follows into the future
Blinded = Investigator, patient and/or sponsor does not know what device was given
Randomized = two or more devices being studied and patients are assigned to one device in an unbiased process (envelope or computerized)
Multi-center = More than one site

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Determining Design of a Clinical Trial

2. What type of patients?

The Patient demographics and characteristics can influence outcomes of a clinical trial/study, such as:

- *Local patient profile considerations*
- *Diabetes*
- *Hypertension*
- *Smoker*
- *AMI (acute Myocardial Infarction or heart attack)*

Note: number of patients in a study can also influence the outcomes of a clinical trial

Determining Design of a Clinical Trial

3. What type of lesions?

Lesion characteristics influence patient outcomes

- *Lesion length: ↑length = ↑events*
- *Vessel diameter: ↑diameter = ↓events*
- *Lesion complexity based on length, vessel bend and degree of blockage (A, B, C type lesion)*
- *Restenosis: reoccurrence of blockage in a vessel*
- *Total occlusions: complete blockage in a vessel*
- *Bifurcations: space where the vessel splits into two pathway*
- *SVG*

Determining Design of a Clinical Trial

4. What type of outcomes?

Outcomes will differ depending on the method of measurement and how it was measured:

- *IVUS (Intravascular ultrasound)*
- *Angiography: measures restenosis and late loss*
- *Clinical: measures death, MI & vessel revascularization*

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Examples of Clinical Evidence

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TAXUS Clinical Program

- Multicenter Studies
- Large Patient Populations
- Independent Monitoring and Adjudication

Comparing U.S. Experience

	TAXUS® Stent	
Pivotal	TAXUS IV Trial	Randomized, Double Blinded
Complex Lesion	TAXUS V Trial	Randomized, Double Blinded
Real World Experience	ARRIVE 1 Registry	Post-Market
Next-Generation DES Trial	ATLAS Trial	Multi-center, Single Arm, Historical Control

Examples of Clinical Evidence

PTCA	DES	PTCA + New
Existing technology	New technology	Indication & Bifurcation
Class III - (US)	Class III – Global	New intended use
Class IIb – (EU)		
-		
-		
- Clinical justification		- Post-market
	Different Stent Design with same formulation?	

Early & often meetings with regulators regarding high-risk products to determine clinical needs

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Thank You

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