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THE REACTAFORUM
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PRECISION MEDICINE - THE FUTURE IS NOW
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The Role of Early Clinic Research/Clinical Pharmacology Trial Centers in Precision Medicine Research

Symposium 7:

Global Initiatives: Collaboration and Best Practices Forum

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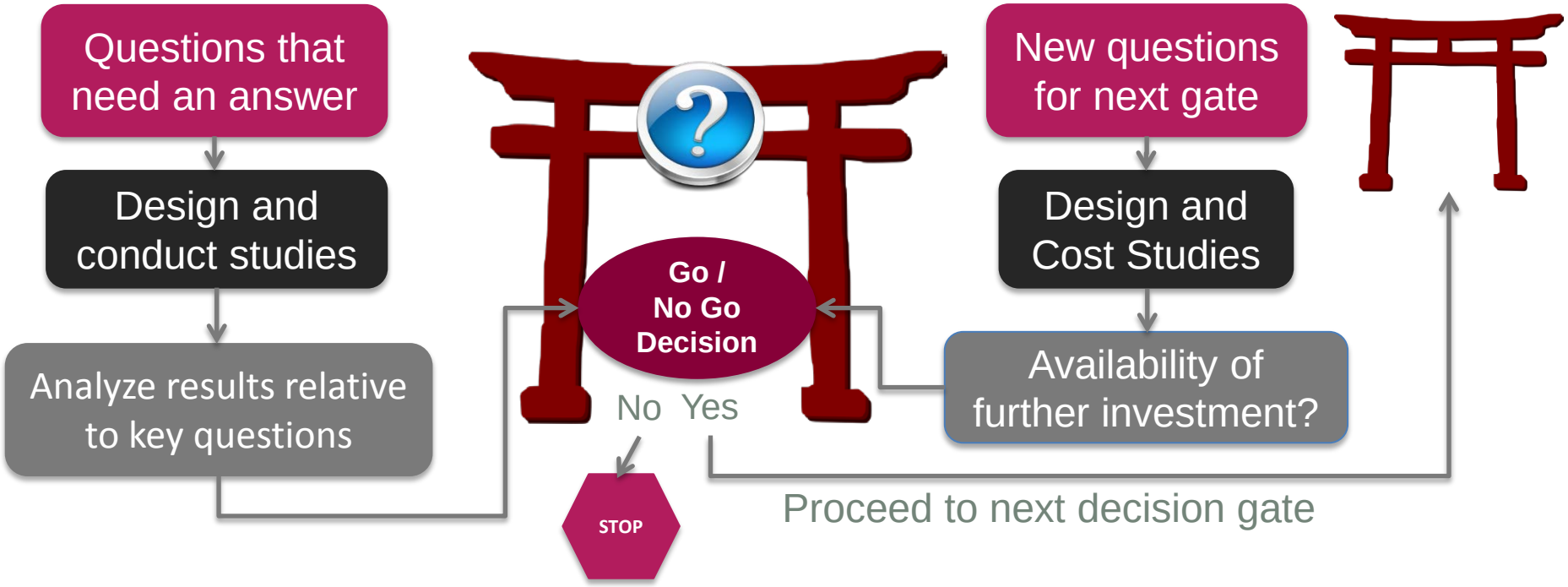
“Decision Gates” in Drug Development



Three Important Factors

- Decision Process → who decides?
- Timing relative to resources, competition
- Quality of Information → role of biomarkers

Go / No Go Decision Gates in Drug Development

Decision Gate	Question	Decision-Maker(s)	Role of Biomarkers
Disease Target	Does a drugable target exist that impacts disease progression?	Scientist	Defining mechanism of action
Lead Candidate	Does a suitable drug candidate exist with properties predicted to impact disease in a positive way?	Scientist Sponsor	Impact on disease Drug delivery to site of action
First-in-Human	Can the drug candidate be given safely to humans?	Sponsor Regulators IRB/EC Investigators	Impact on disease Safety measures of clinical relevance
Clinical Proof-of-Concept	Does the drug work in humans as it was designed?	Sponsor	Confirming mechanism of action in humans Impact on disease Defining dose-limiting toxicity
Begin Phase 3	Can dosage, target patient populations, and pivotal efficacy and safety study designs be justified?	Sponsor Regulators	Impact on disease / dose-response Patient selection Patient safety
Marketing Application	Has safe and effective use of the drug been proven?	Regulators	Validated markers that may contribute to the confirmation of safety and efficacy
Postmarketing Safety	Are there emerging safety issues that need further action?	Sponsors Regulators	Predict patients more likely to experience rare events

Biomarkers Provide Data That Enable Better Decisions Early in Drug Development

- **Efficacy** Biomarkers – help establish "proof of mechanism" or "clinical proof-of-concept"
  - Specific for therapeutic target
- **Safety** Biomarkers – provide sentinels of toxicity
  - Apply broadly across therapeutic areas
  - Most useful if can catch serious toxicity early
- **Patient Selection** – allow investigators to choose likely responders over likely non-responders
  - Enriched responder cohorts reduce clinical study size
  - Form the basis for companion diagnostic tests

Important "Proofs" in Early Clinical Research
Key Role of Biomarkers

- **Proof-of-Presence (Phase 1)**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism (Phase 1 or 2)**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept (Phase 2)**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

- Pharmacokinetics
- Tissue concentrations
- Healthy subjects (HS) or patients

- Biomarkers reflecting target engagement
- Biomarkers of toxicity (liver, kidney effects)
- Healthy subjects or patients

- Biomarkers reflecting impact on disease
- Biomarkers of toxicity (liver, kidney effects)
- Patients

Highly Targeted Drugs – Easier or Harder?

	Easier	Harder
Specificity of Effect	Fewer off-target effects → fewer AEs	Possible high potency and steep dose-response curve → more difficult dose escalation
Biomarkers	Can be specific → provide valuable data for CPoC study	Often need to develop unique assays
Recruitment	If standard of care is poor, attractive to patients and investigators	Difficult to find the right patient if other options exist
Conduct	Promising targeted drugs will attract quality investigators	Complex sample and patient logistics
Regulatory	Orphan classification can provide faster time to approval	May require companion diagnostic tests

Strategic Approach: Build a Bridge Backwards

Start design of CPoC study first

- What is “Proof”? Endpoints?
- What patients? How many?

How to get to CPoC?

- What can I do in healthy subjects?
- Are biomarkers available?
- Develop novel biomarkers?
  - Biochemical assays
  - Imaging and imaging agents
  - MicroRNA panels
- Would microtracer studies be valuable?
- Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?

The Three Constraints

Early Signals of Clinical Safety and Efficacy are the Key to Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

Patients

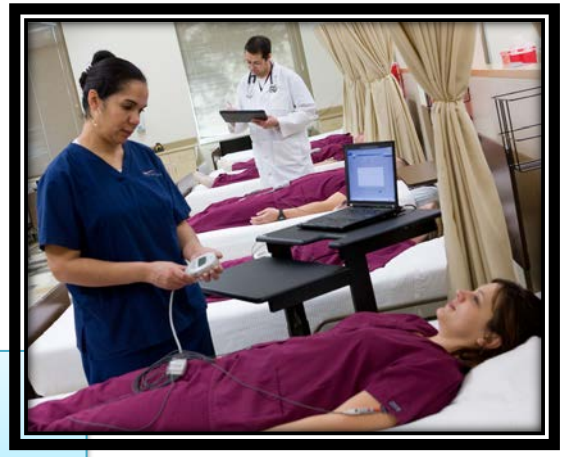
- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

Investigators / Clinical Trial Units

- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global GCP standards
- Ethical

Clinical Trial Units Must Have:

Facilities for confined studies in a highly controlled environment

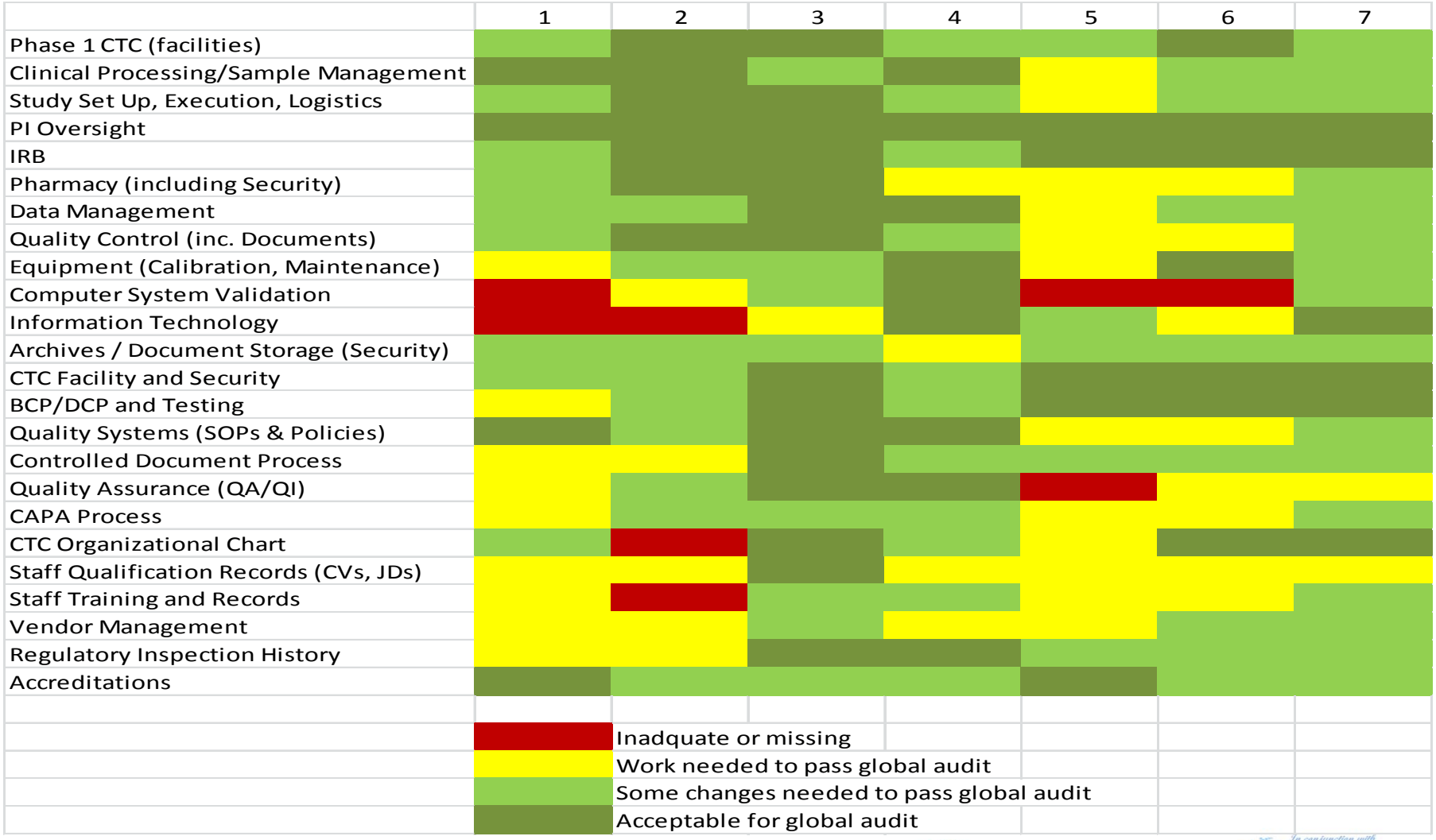


Well trained staff competent in GCP regulations

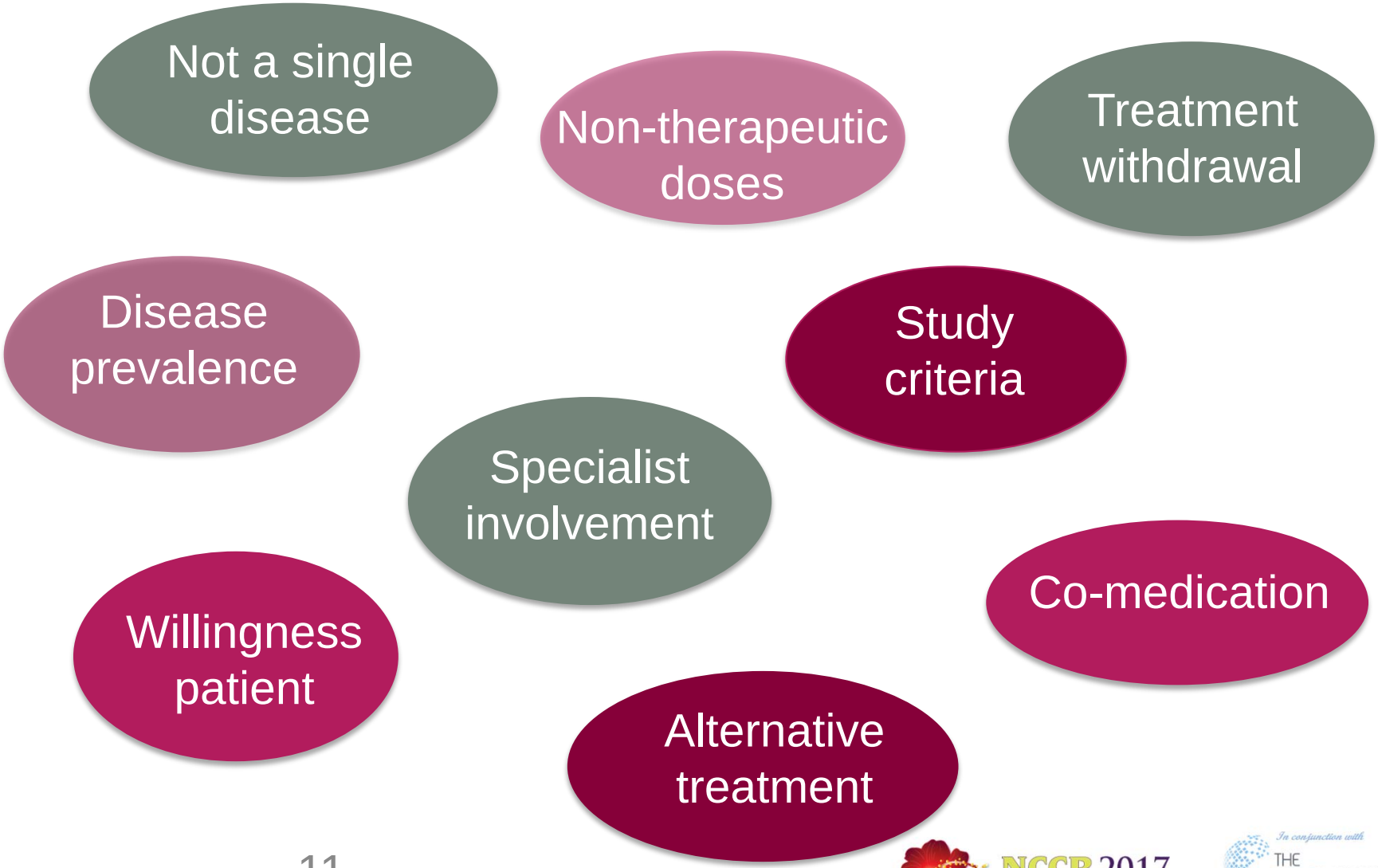
Access to patients suitable for early clinical research studies

Ability to manage the logistics of complex, time-dependent procedures

Celerion Audit Results of 7 Asian CTCs 2013-2014

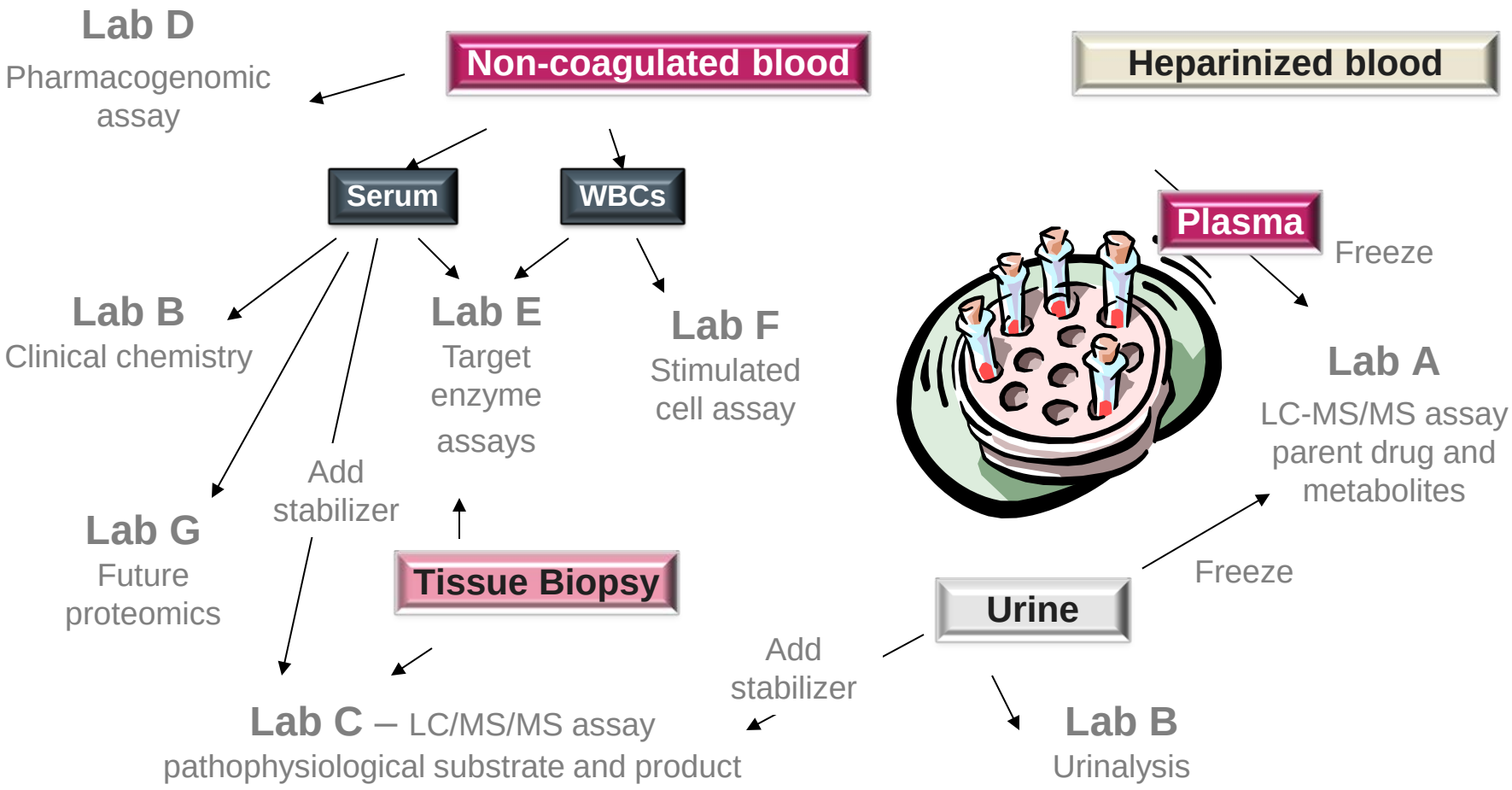


Challenge: Recruiting Patients to Early Clinical Research Studies



Challenge: Complex sample collection schedules and processing procedures

Example: First-in-Patient study – 14 tests, 7 labs



Specialty Clinical Trial Units

Celerion's Respiratory Center of Excellence

Belfast, UK

Spirometry

Bronchoalveolar Lavage

Challenge Models

Body Plethysmography

Fractional Exhaled Nitric Oxide Testing

Lung Clearance Index

Take Aways

- Precision medicine means more targeted drugs → less off-target effects → safer
- Early clinical research challenges include:
  - finding the right subject or patient
  - right biomarkers to demonstrate target selectivity
  - managing controlled clinical studies with complex sample logistics
- Specialized clinical trial units offer a good solution for early studies with precision medicines.

Terima Kasih

Thank You

Daedanhi Kamsahamnida