Alliance for Clinical Research Excellence and Safety

Enhancing Safety, Quality and Efficiency in Drug Development and Health Science

A Proposal:

APPLICATION OF SAFETY ENGINEERING ('STAMP') TO THE SYSTEM FOR "FIRST IN MAN" CLINICAL RESEARCH

2nd STAMP European Workshop, University of Stuttgart, Germany

9.00-9.30 Day 2 September 23rd 2014

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http://www.acresglobal.net/

THE OBJECTIVE OF ACRES

Not for profit voluntary global organisation based in the US but with international regional development

Transform the world of clinical research so clinical trials are responsibly conducted according to the highest standards of safety, quality and efficiency.

Special thanks to Erica Elefant, Jonathan Fishbein and Irina Colligan for contributions to these slides

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AIM OF TODAY'S PRESENTATION

I. Provide an overview of entire drug development process
II. Provide information on (some of) the players within each system
a. Regulatory agencies
b. Ethics committees
c. Sponsors in many guises
d. Supporting organisations: CRO/other vendors
e. Investigator Sites
III. What is required to get a First into Human study up and running?,
IV. What are the current safeguards in place:

V. What are the concerns ?
VI. How might this relate to STAMP?

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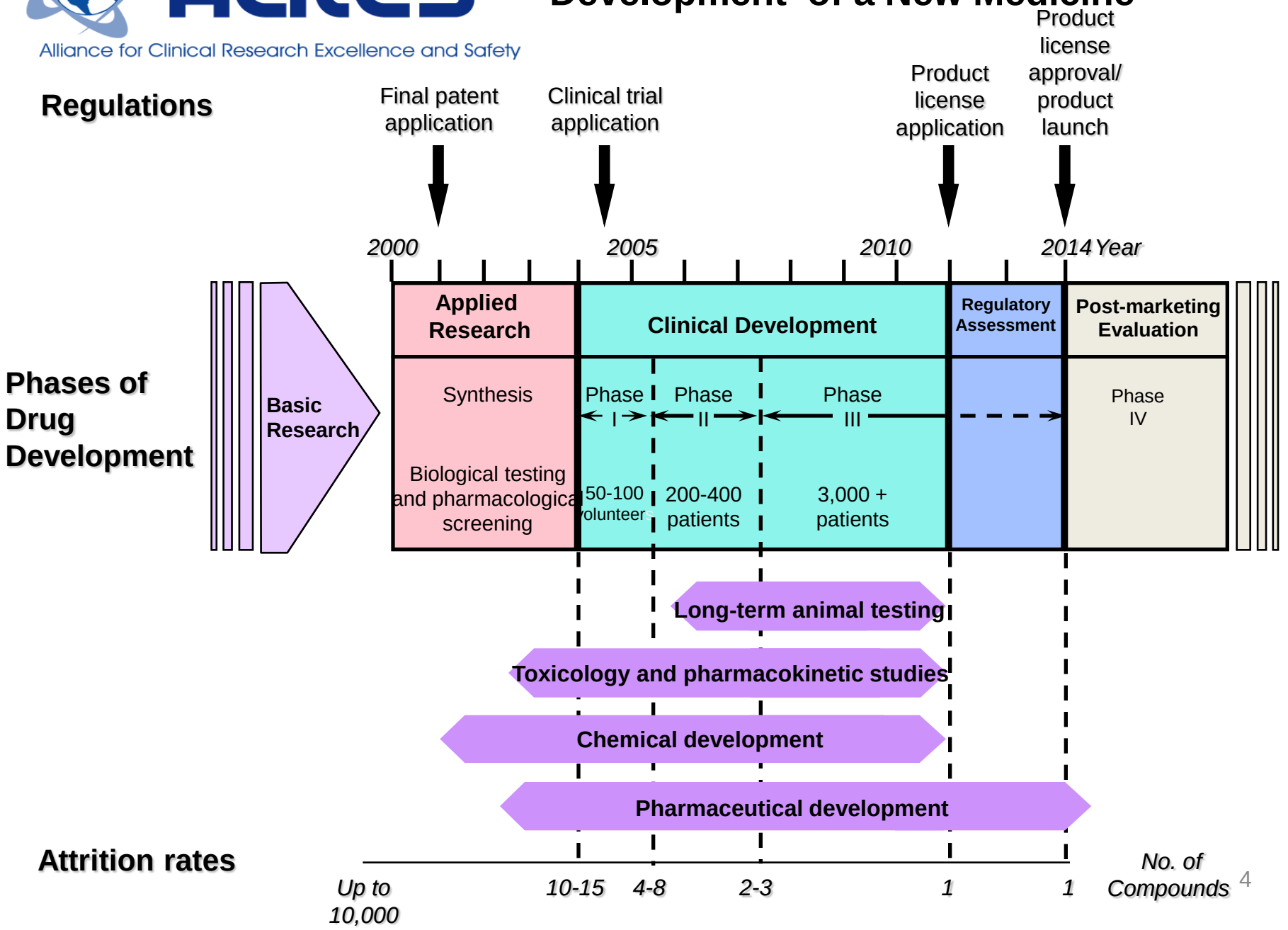
Stages in the Discovery and Development of a New Medicine



DRUG DISCOVERY AND DEVELOPMENT SINCE 1950'S

- Rational design
- Serendipitous
- Based on natural products
- Empirical

Pharmaceutical Research: How does it all start?

➢ Biologists

- Identify targets
- Carry out biological assessment of new chemical compounds
  - High throughput screening
- Develop secondary assays

➢ Chemists

- Identify chemical lead
- Carry out structure activity relationship view a view to
- Lead optimisation

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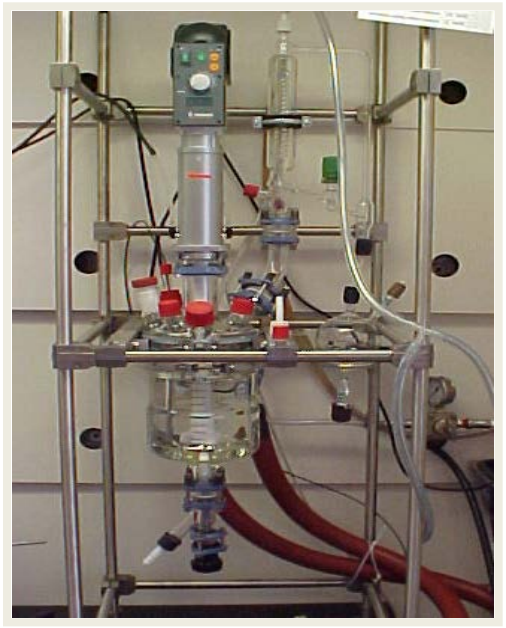
The ‘investigational medicinal product’



All medicines contain more than the active drug !

For early studies ‘product’ may be assembled on site (brings its own risks)

- ACTIVE DRUG
- Related substances
- Process residues
- Degradation products
- Excipients
  - Other active materials
  - ‘Extractives’

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The toxicology process

- Toxicology is a collaborative process
  - 'Absorption, Distribution, Metabolism & Excretion'
  - Pharmacology
  - Pharmacy, Synthetic & Analytical Chemistry
  - Quality Assurance
  - Clinical Pharmacology & Research

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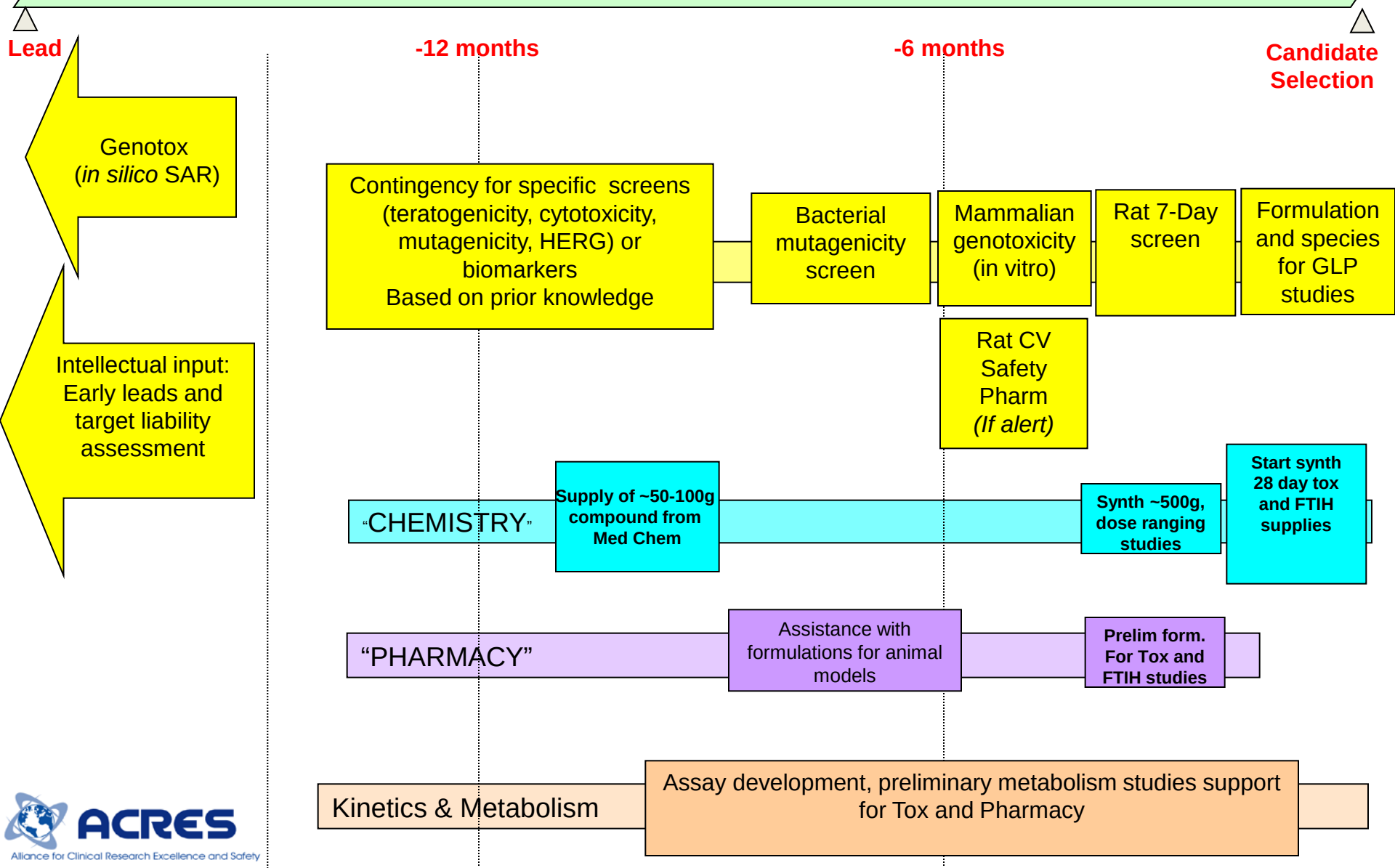
What goes on before a medicine gets into Man?



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Safety Assessment in Phase 1: First into man

- Provide sufficient safety data to support dosing at the required phase
  - No clinical data (usually if novel)
  - Low dose: stopping rules
  - Careful escalation and frequent assessments
  - Small numbers: volunteers or patients

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Study Results And Observations

- In an ideal world a Study might give you :
  - Dose(s) that produce no effects
  - Dose(s) that produce acceptable effects
  - Dose(s) that produce overt toxicity

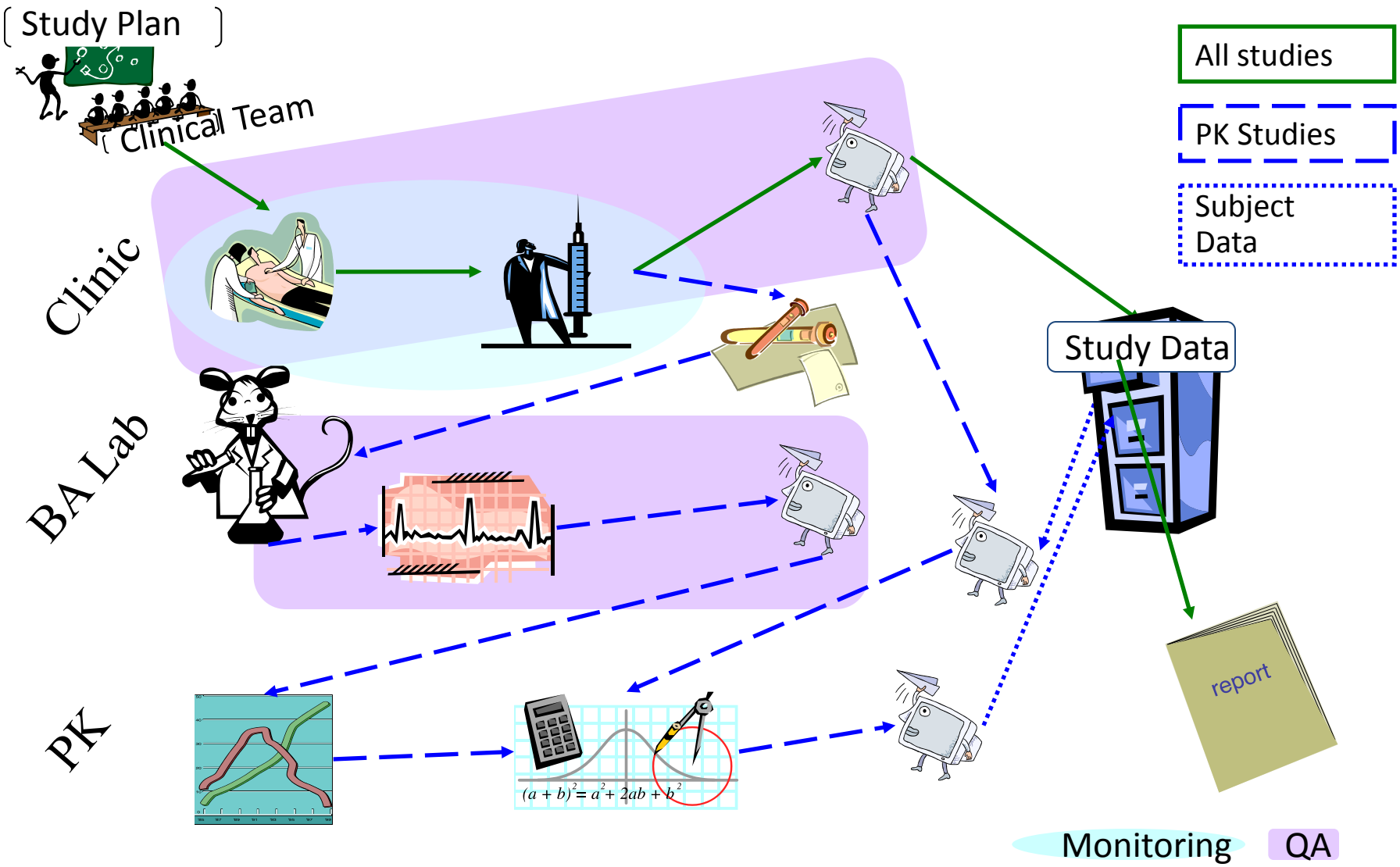
No Observable Effect Level (NOEL)

No Observed Adverse Effect Level (NOAEL)

Effects and interpretation

- Are there margins of safety for humans ?
- Changes may be toxicologic
- Changes may be pharmacologic
- What do the changes mean?
- Species idiosyncrasies
- Can potential changes be monitored in man?

THREE VIEWS OF A FIRST-INTO-MAN STUDY
1 - Chronological



THREE VIEWS OF A FIRST-INTO-MAN STUDY
2 - Process Mapping

Study Planning & Set Up

Clinical Phase

Data Analysis

Reporting

Archival

Protocol

Selection & preparation of sites

CRF / data collection tools

Outsourcing

Informed Consent

Stats analysis plan, Data Management Plan, etc.

Clinical Supplies

Other "stuff": biomarkers, kits

Dosing, Observation

Site Monitoring

Study Assessments

Data Management

Statistics

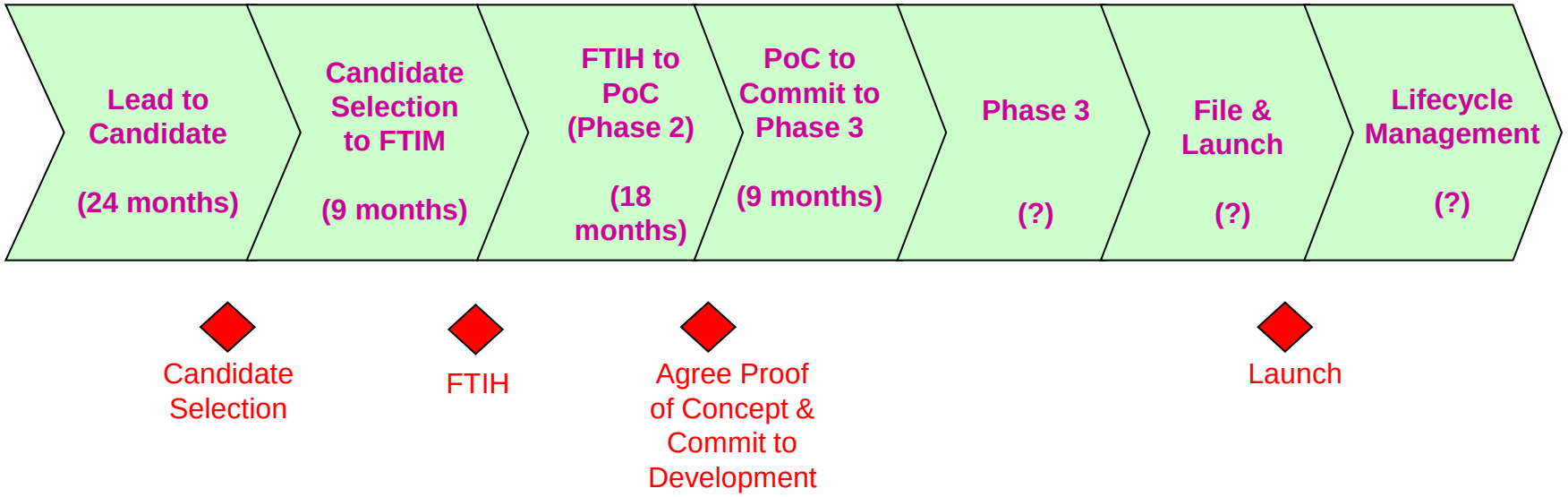
Safety

Clinical Study Report

Archive Records

Pharmaco-kinetics/dynamics

Highly Idealised Development Process: Phases and Decision Points



- FTIH = First time in humans (Initially single doses, then for several days)
- Phase 2 = Limited patient trials (Defining the appropriate doses for efficacy & safety)
- PoC = Proof of Concept (Is the drug likely to work!)
- Phase 3 = Full-scale patient trials

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THREE VIEWS OF A FIRST-INTO-MAN STUDY
3 - A Team Effort

CLINICAL SITE

Treatment / Dosing of Subjects

Sample Collection & Processing

Sample Storage & Shipment

PROTOCOL

Sample Handling

Clinical TEAM

Analytical Method
Equipment
Analysts

Sample analysis

BIOANALYSIS

Data Analysis (incl. PK/PD)

Different Regulatory Scenarios drive development

Different Scenario
New chemical entity • First Authorisation
New combinations • one existing product and a new chemical entity • two existing products • two existing products (new indication and new route)
Existing product • new strength • new route • new form • new indication
‘Reformulation’ • Standard Generic • Non standard Generic • Well-established use • Biosimilar

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Regulations drive development

Scenario	EU Legal Basis	US Legal Basis
New chemical entity		
• First Authorisation	Article 8(3)	21 CFR §314.50
New combinations		
• one existing product and a new chemical entity	Article 8(3)	21 CFR §314.50 and §300.50
• two existing products	Article 10b	21 CFR §300.50
• two existing products (new indication and new route)	Article 10b	21 CFR §300.50 and 314.70
Existing product		
• new strength	Line extension	21 CFR §314.70
• new route	Line extension	21 CFR §314.70
• new form	Line extension	21 CFR §314.70
• new indication	Type II variation	21 CFR §314.70
'Reformulation'		
• Standard Generic	Article 10	505(j) and 21 CFR §314.94
• Non standard Generic	Article 10(3)	21 CFR §310, §314 and §320
• Well-established use	Article 10a	505(b)(2) & 21 CFR §314.54
• Biosimilar	Article 10(4)	BPCI – §7001 *

* Implementation Pending

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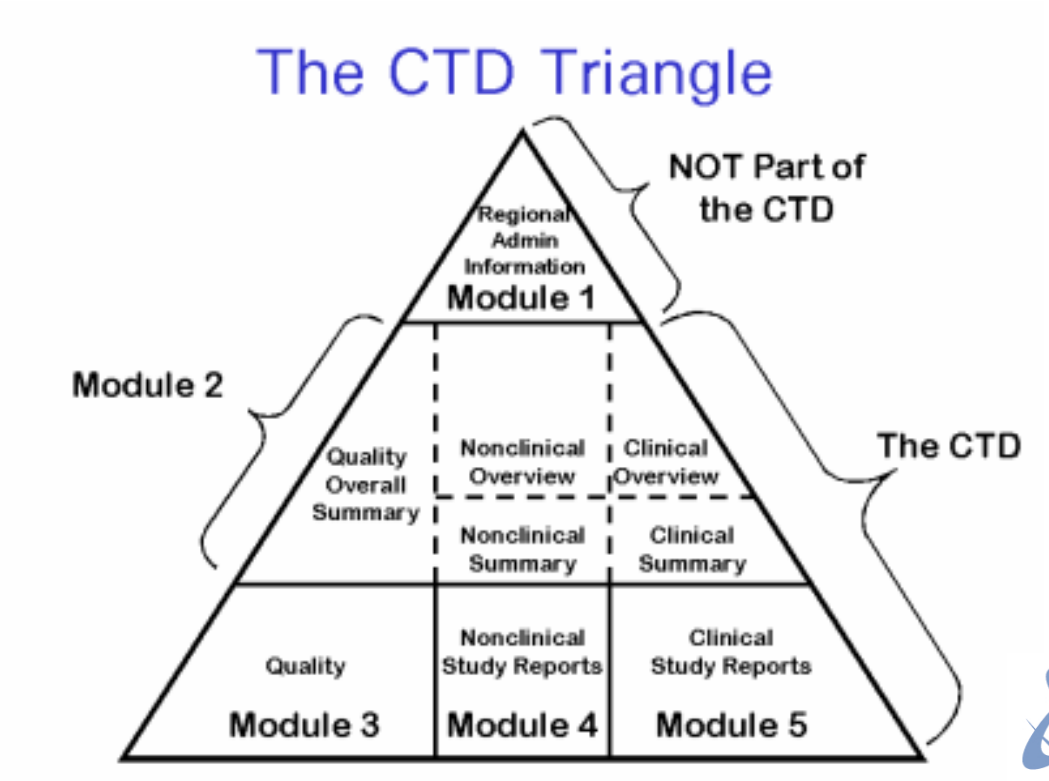
The End Game: Dossier Requirements
Explanation of CTD Modules

- CTD = Common Technical Dossier valid in EU and USA



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So what Clinical Development Accident Terminology do we have ?

Adverse Event (AE) = Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR) = Any untoward and unintended response to an investigational medicinal product related to any dose administered. This implies reasonable causal relationship

Serious Adverse Event (SAE) = Any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

SUSAR = Suspected Unexpected Serious Adverse Reaction

Quality management terminology such as Deviations and violations *BUT Accident has not been defined*

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So why the need for change ?

- Too often regulation for clinical research are reactions to safety issues rather than being prospectively designed based on evidence
- Excellent regulations but implementation is focussed on compliance leading to ‘risk aversion’
- Regulations are added without a holistic view of how they impact the system
- No known attempts to apply organisational science techniques
- Concerns about less than rigorous methodology and compliance in less regulated territories
- Concerns about volunteer remuneration, lack of informed consent, informed consent under duress, coercion, ‘professional volunteer’
- No tracking between First into Human study sites: all act independently
- Compressed timelines/decreased budget due to the competitive and for profit nature of drug with competitors working on similar targets
- FIH studies are becoming increasingly complex (i.e. additional assessments; trying to learn more early in development)
- Examples of expedited timelines and too few resources stressing the system

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So what are we proposing…..?

Evaluate whether STAMP Methodology can help us better described the an ideal first- into-man system in clinical research

Help us identify the strength and weaknesses of current approach

Identify what we are trying to achieve through risks management

- Better hazard definition
- Consensus about accident to be avoided

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The Three Steps to define the First into Man System

- Develop specific goals for first-in-man; identify domains of interest and case studies
- Model the current systems in place by means of collaboration through ACRES
- Convene Subject Matter Experts from clinical development and STAMP engineers to determine potential approaches for improvements to the processes as regards risks, hazards and accident definitions

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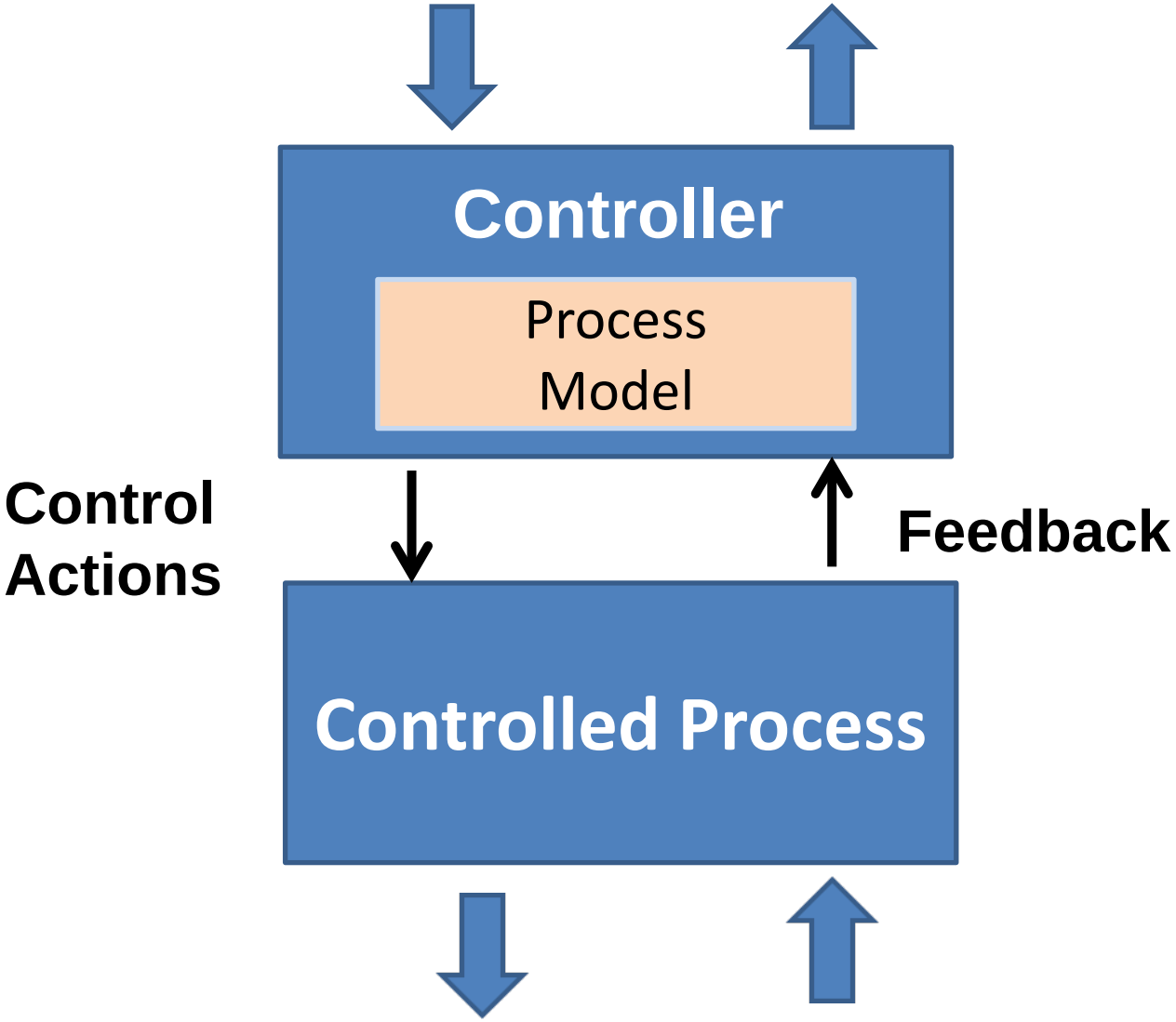
Why might STAMP help define the First into Man system?

STAMP Model

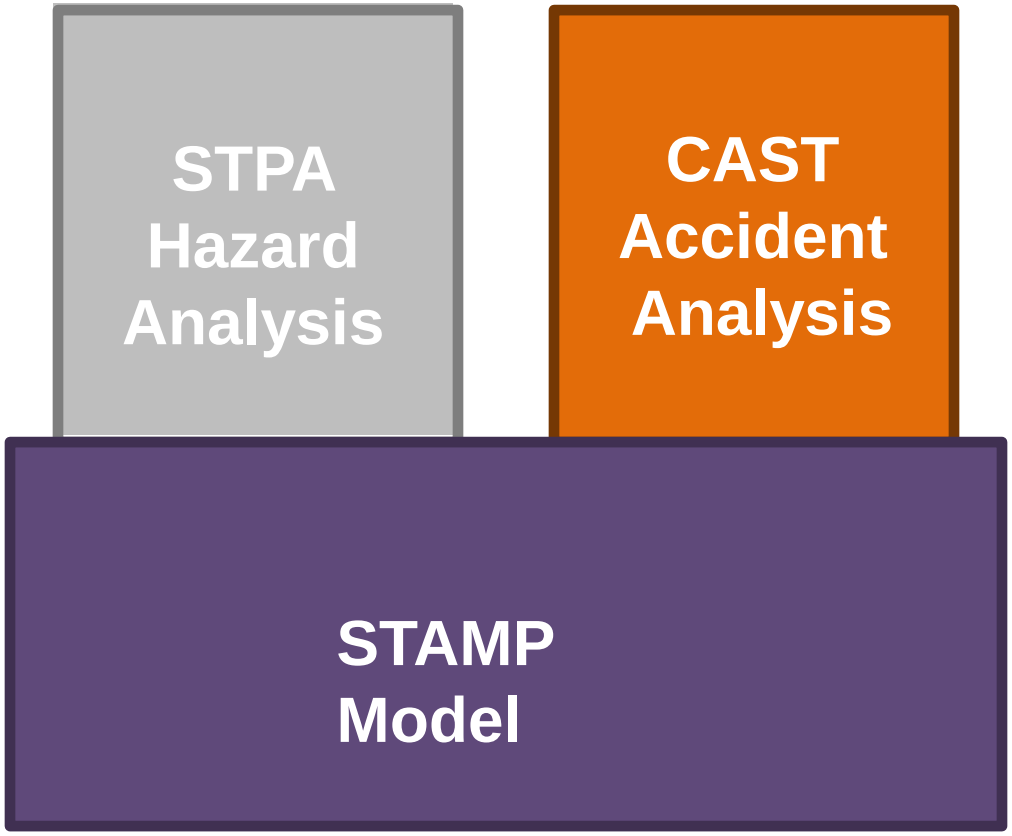
- Clinical research is certainly a collection of complex dynamic **processes**.
- Currently when something serious go wrong, it is a process failure with someone to blame: not seen as a **control problem**
- We do not know what are the constraints on component behavior and **interactions**
- We hope STAMP will allow us to identify more root causes:
  - Component failure in linking processes
  - Unsafe interactions among components
  - Complex human, software behavior
  - Design errors in experiments, trial
  - Flawed requirements

    - in appropriate application of regulation

Basic Control Loop



Hazard and Causal Analysis using System Theory

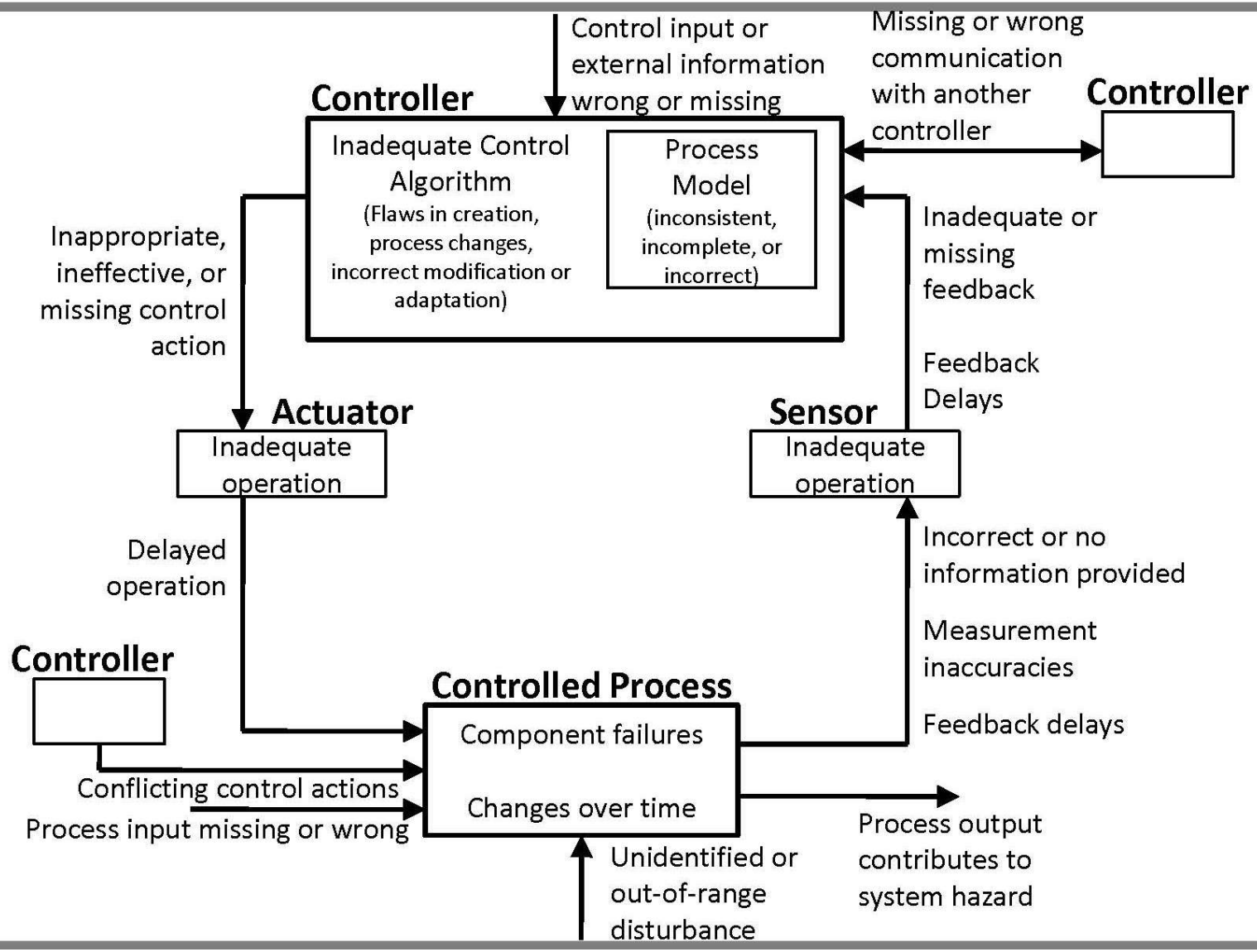


Concept of ‘inadequate control’ and accident novel
Focus on product not the system

Risk aversion because we do not know where all controls are

(Leveson, 2011)

Step 2: STPA Control Flaws



Identify Unsafe Control Actions

	Action required but not provided	Unsafe action provided	Incorrect Timing/ Order	Stopped Too Soon / Applied too long
Action (Role)				

The ideal system for safe clinical research: what are we looking for today?

WE NEED YOUR HELP...we cannot do this alone

Expertise outside of Biomedical R&D is crucial to success to creating a safety culture in our business sector

- Dissect the First into Man system into bite-sized chunks : ‘ domains’
- Identify Case Studies
- Workshop between Clinical R&D and STAMP engineers to assess feasibility using STAMP, its strengths and weaknesses and what the ’toolkit’ might look like
- Design pilot projects based on proposed protocol with metrics such as ’time’
- There will be intractable domains so this will be messy but we’ll learn alot !
- Increased likelihood of funding if a multidisciplinary team

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