Grand Challenges
African Drug Discovery Accelerator

An overview of first-in-human trials including analytical considerations in the design, analysis and interpretation of clinical studies

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14th February 2025

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Overview

1. Introduction to first in human trials
2. Preclinical safety testing
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4. Study design considerations in FIH trials
5. Biomarker assessment
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8. Conclusion.

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1. Introduction to First in Human Trials

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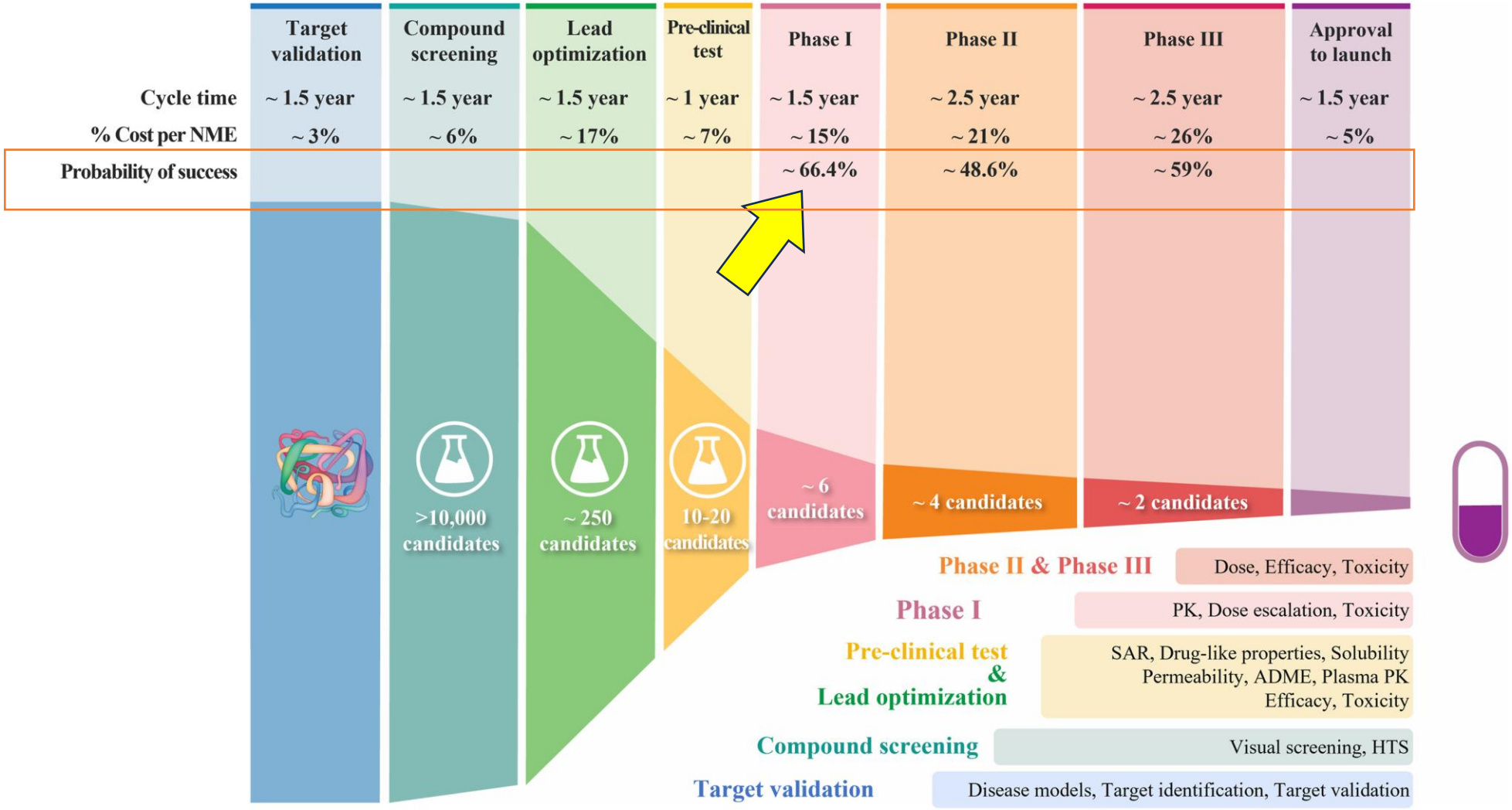
First-in-Human Trials: Where Science Meets Caution

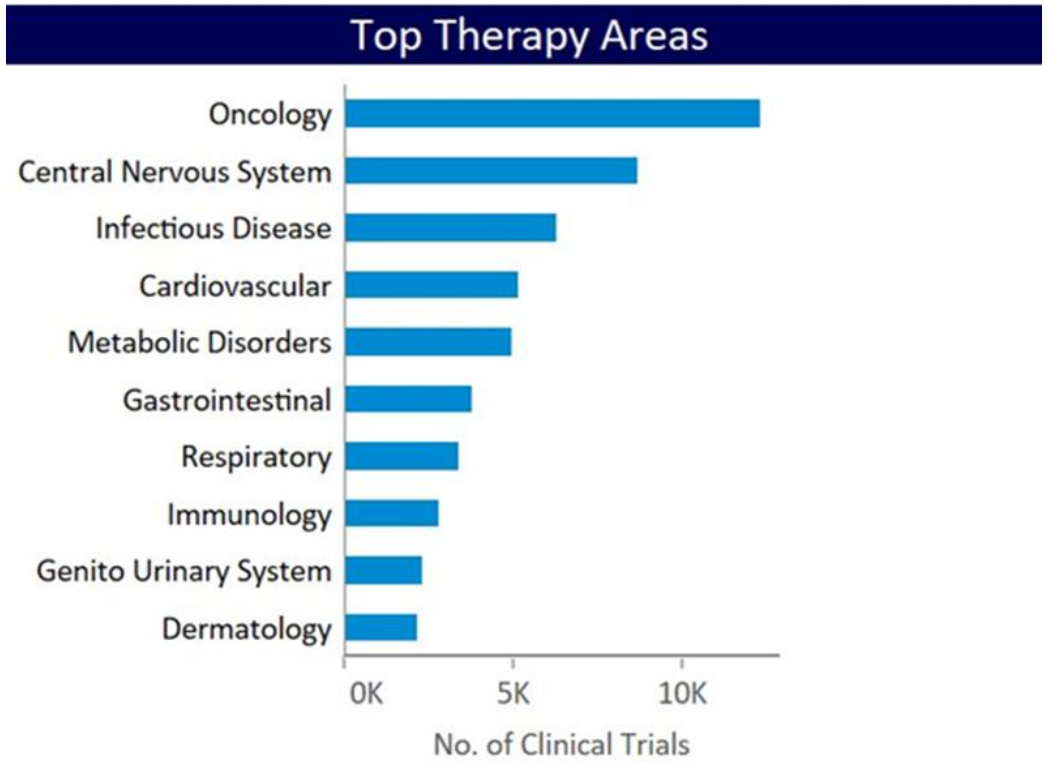
- FIH trials (Phase 1) are the first human testing of a new drug, bridging preclinical data to real-world application.
- Focus on assessing safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD), ensuring no unexpected outcomes.
- Conducted in small groups of healthy volunteers or patients, using dose escalation methods for safety.
- Rigorous monitoring with sentinel dosing and early stopping criteria to minimise risks.
- If successful, the drug advances to Phase 2; if not, it returns to the drawing board, balancing hope and caution.

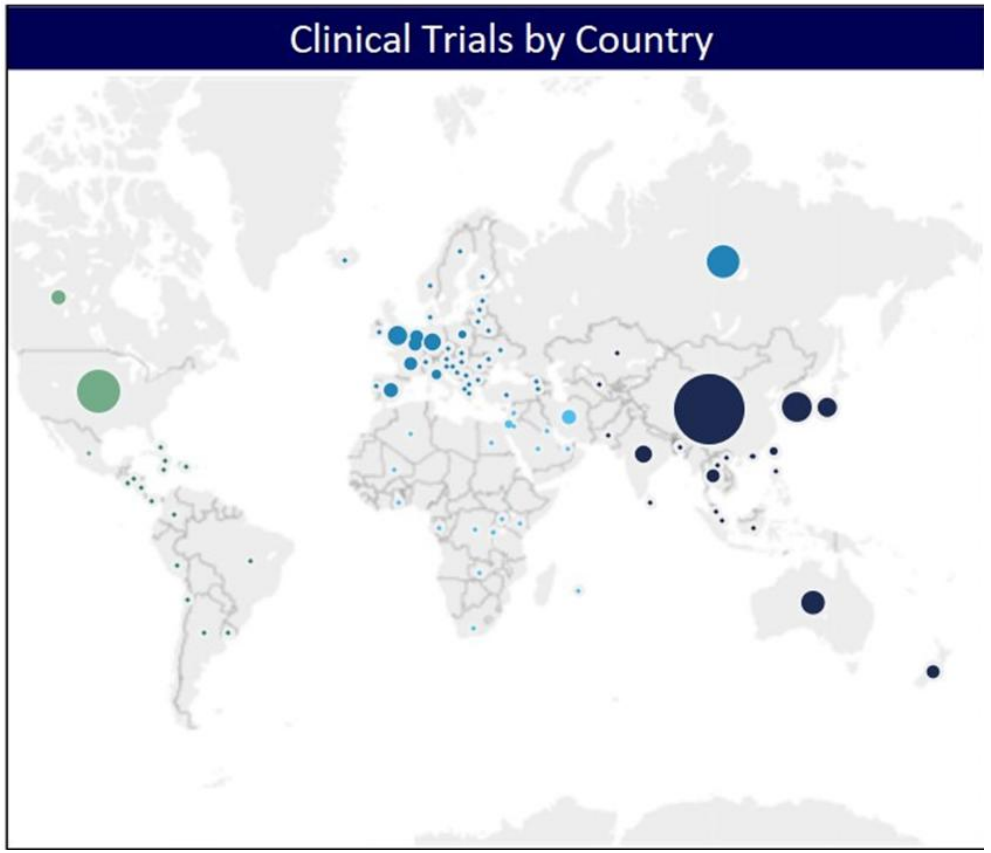
On the rough road to success……



Duxin Sun.et al . Why 90% of clinical drug development fails and how to improve it?,Acta Pharmaceutica Sinica B, Volume 12, Issue 7

First in human trials: Location and therapeutic areas, but where is Africa?





Sources: globaldata.com, clinicaltrials.org

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2. Preclinical safety testing for FIH trials

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Preclinical safety testing for FIH trials

Key Guidelines and Regulatory Background:

- **ICH Guidance**:
  - *ICH M3(R2)*: Core safety evaluation expectations for FIH trials.
  - *ICH S6(R1)*: Biologics-specific requirements.
  - *ICH S9*: Guidelines for anticancer pharmaceuticals.

Goals of Preclinical Safety Testing:

1. Identify organ toxicity and relation to drug exposure.
2. Assess on-target and off-target effects.
3. Determine relevance to human safety.
4. Identify and qualify biomarkers for clinical monitoring.

Considerations in Safety Testing Strategy:

- **Therapeutic Type**: Different approaches for small molecules vs. biologics.
- **Therapeutic Indication**: Tailored assessments for specific disease areas (e.g., CNS, oncology).
- **FIH Trial Design**: Align preclinical studies to match trial scope, treatment duration, and patient/volunteer safety needs.

Preclinical Safety Study Design

- **Study Requirements by Therapeutic Type**:
  - **Small Molecules**: Genotoxicity (ICH S2[R1]) and QT assessment for cardiac safety.
  - **Biologics**: Non-rodent species, focus on pharmacologic relevance.
- **Core Safety Protocols**:
  - **Toxicology**: MTD, NOAEL, and dose-ranging in animals.
  - **Safety Pharmacology**: Cardio (QT prolongation), CNS, respiratory systems.
  - **Photosafety**: Initial phototoxic potential assessment (ICH S10).
- **Alternative Routes**:
  - Exploratory trials (microdosing up to 14-day): Early PK, PD, biomarker data.

ICH recommended preclinical studies enabling FIH trials(1)

Study type	Small molecules	Large molecules	GLP compliance Requirement
Pharmacodynamics			No
In vitro (MOA)	X	X	
In vivo (MOA and therapeutic effect)	X	X	
Safety pharmacology (ICH S7A62 and S7B63)			Yes
In vitro (concentration-effect relationship)	X	X	
In vivo (dose-response for CNS, CV, respiratory effects)	X	X	
Pharmacokinetics (ICH M3(R2)6)			
In vitro metabolism (across species microsomal metabolism)	X	NA	No
In vitro plasma protein binding	X	NA	No
Toxicokinetics from repeat dose GLP toxicity studies (ICH S3A64)	X	X	Yes

Shen, J., Swift, B., Mamelok, R., Pine, S., Sinclair, J. and Attar, M. (2019), Design and Conduct Considerations for First-in-Human Trials. Clin Transl Sci, 12: 6-19. https://doi.org/10.1111/cts.12582

ICH recommended preclinical studies enabling FIH trials(2)

Study type	Small molecules	Large molecules	GLP compliance Requirement
Genotoxicity battery (ICH S2(R1)7)			Yes
In vitro Ames test	X	*	
In vitro and/or in vivo mammalian cell chromosomal damage evaluation	X	*	
Single-dose / dose range finding			No and Yesc
Rodent single-dose (could be MTD study)	X	NA	
Nonrodent single-dose (could be MTD study)	X	X	
Repeat dose toxicity (ICH M3(R2)6)			Yes
Rodent multidose	X	Optional	
Nonrodent multidose	X	X	
Other studies			No
Immunotoxicity (ICH S865)	X	X	
Photosafety (ICH S1010)	X	X	

Shen, J., Swift, B., Mamelok, R., Pine, S., Sinclair, J. and Attar, M. (2019), Design and Conduct Considerations for First-in-Human Trials. Clin Transl Sci, 12: 6-19. https://doi.org/10.1111/cts.12582

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3. Starting dose selection in FIH trials

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Starting Dose Selection for FIH Trials

- **Objective**: Define an initial dose range based on preclinical results (pharmacology, toxicology, PK data) and any relevant human data on similar mechanisms of action (MOA).
- **Key Considerations**:
  - Starting dose must balance **toxicity risks** with the need for **pharmacologic activity**.
  - **Dose range** should include escalation steps to inform later efficacy-focused studies.
  - Avoid too low starting doses or overly cautious escalation to prevent unnecessary cohorts that can increase study size and duration.
- **Regulatory Guidance**:
  - **EMA**: Covers preclinical to clinical transition, risks, and mitigation in FIH trials.
  - **FDA**: Suggests using NOAEL as a benchmark for a safe starting dose based on toxicology data.

FIH Dose Selection

- **No Standard Approach**: Each drug candidate has unique considerations, making a single dose selection method impractical.
- **Common Methods**:
  1. **Empirical Approach (FDA)**:
     - Uses NOAEL with allometric scaling for a maximum safe dose.
     - Pros: Low toxicity risk. Cons: May miss active pharmacologic dose, doesn't address dose escalation.
  2. **Mechanistic Approach (EMA)**:
     - Utilizes detailed preclinical pharmacology data, ex vivo/in vitro studies, and modeling.
     - Focuses on **Minimal Anticipated Biological Effect Level** for more targeted, potent therapies, often at doses lower than NOAEL.

Regulatory frameworks provide a structured yet adaptable model for safe, effective FIH starting doses.

FIH Dose Selection (small molecules)

2 primary approaches to interspecies scaling of small molecules

- **Allometric Scaling Modifications:**
  - Rule of Exponents
  - Liver Blood Flow Correction
  - In Vitro Metabolic Clearance Correction
- **ICH S9 Guidance for Anticancer Agents:**
  - Starting dose based on toxicity in animals.
  - Consider highest non-severely toxic dose (HNSTD) rather than NOAEL.

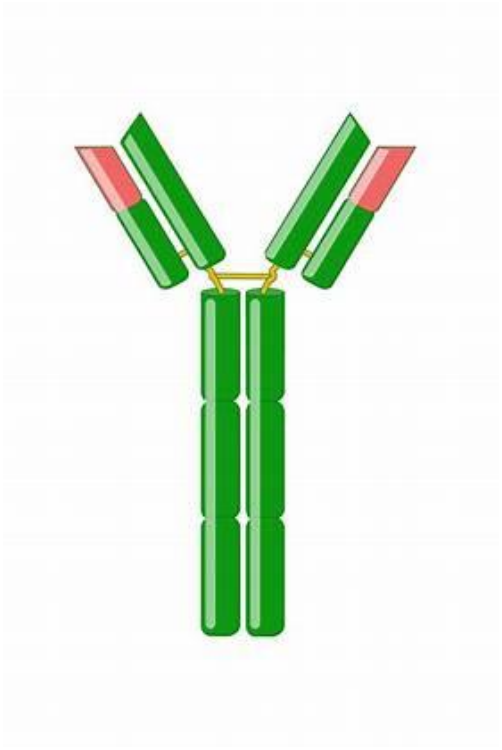
Physiological-Based Pharmacokinetic (PBPK) Modeling:

- Mechanistic, but data-intensive.

Allometric Scaling:

- Empirical, less data-intensive, but less accurate for compounds with high cross-species variability

FIH Dose Selection (large molecules)



- **Biodistribution and Pharmacokinetics considerations**
  - **Polarity, Charge, Molecular Size**
  - Primarily eliminated via **renal excretion** and **proteolytic degradation** to amino acids.
  - Allometric scaling methods are effective due to conserved processes across mammalian species.
- **Pharmacokinetics of Monoclonal Antibodies (mAbs)**:
  - Predictive models rely on PK data from **nonhuman primates**.
  - **Linear PKs**: Simple allometric scaling predicts human PK within a twofold range.
  - **Nonlinear PKs**: Overestimation occurs at sub-target-saturating concentrations; consider target-mediated parameters for accuracy.
- **Local Delivery Considerations**:
  - Similar scaling principles apply but may require PBPK approaches due to challenges in validating target site PK in humans.

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4. Study design considerations in FIH trials

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Sample Size and Inclusion of Placebo Subjects in FIH Trials

- **Typical FIH Design:** Blinded, placebo-controlled with 8-10 subjects per cohort (3:1 or 4:1 active:placebo) in multiple dose escalation cohorts.
- **Focus:** Safety Signal Detection, not Hypothesis Testing.
- **Detectable Event Rate:** Determined by total subjects, cohort size, event rate, and background rate.
- **Cohort Size (N):** Increasing N from 1 to 6 improves event detection, minimal gain above N=10.
- **Placebo Inclusion:** The rationale for inclusion of placebo-dosed subjects is the perceived bias in adverse event (AE) reporting.

Study Population in FIH Trials

- **Healthy Subjects vs. Patients:** Evaluate risk-benefit for each study.
- **Higher Risk Agents:** Patients might be considered (e.g., life-threatening diseases).
- **Healthy Subjects:** Mitigate confounding factors (comorbidities, medications).
- **Sex Inclusion:**
  - Traditionally: Male volunteers and non-childbearing females.
  - Modern Approach: Include females to understand sex differences in PK/safety/response.

Dose and Dose Escalation Scheme in FIH Trials

- **Mitigate Risk:** Sequential dosing with observation periods between subjects (sentinel dosing).
- **Balance Safety and Defining Correct Dose Range:** Avoid abandoning potentially useful drugs.
- **Maximum Exposure Level:** Predefined for FIH trials in healthy volunteers.
- **EMA Guidance:** Stop dose escalation at pre-defined maximum exposure (Cmax or AUC).
- **Oncology Trials:**
  - Single subject at low dose for initial safety and PK assessment.
  - Body size-based dosing might not be necessary.
- **Dose Finding Designs:**
  - Rule-based (e.g., 3+3 design) or model-based (adaptive Bayesian models).
  - Goal: Identify "Recommended Phase II Dose".

First-in-Human Study Design: SAD/MAD & Adaptive Approaches

- **Traditional Design**:
  - Separate **Single Ascending Dose (SAD)** and **Multiple Ascending Dose (MAD)** studies, with MAD lagging behind SAD.
- **Adaptive SAD/MAD Combo Design**:
  - Conducts SAD and MAD in parallel with adaptive cohorts to test new doses.
  - **Benefit**: Reduces timeline by up to 12 months.
  - **Challenge**: Requires strict safety start/stop criteria.
- **Key Assessments in FIH Studies**:
  - **Food and Formulation Effects**: Often tested at therapeutically relevant doses in SAD arm with **crossover designs** for meaningful results.
  - **Drug-Drug Interaction (DDI)**: Considered if candidate shows strong DDI potential (e.g., cytochrome P450 inhibition) to inform clinical relevance.
- **Immunogenicity**:
  - Essential for **high-risk protein therapeutics**; animal studies aren't predictive, making FIH critical for gauging immune responses.

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5. Safety monitoring in FIH trials

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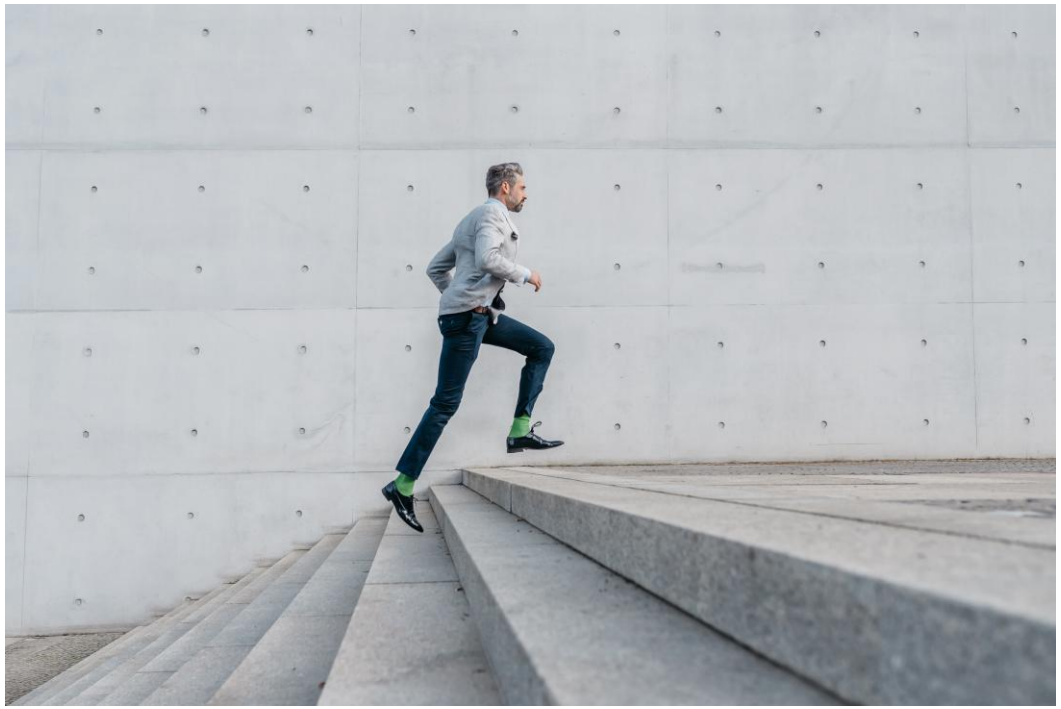
Safety Monitoring in FIH Studies – Key Challenges & Approaches

- **Safety Signal Detection**:
  - Small sample size limits certainty in detecting safety signals.
  - Determining causality is complex, especially in patient populations with high noise-to-signal ratios.
- **Data Collection**:
  - Standard assessments include physical exams, vital signs, lab tests (hematology, chemistry, urinalysis), and ECGs.
  - Additional tests (e.g., ophthalmologic, psychometric) may be required based on **preclinical toxicology**.
  - **Special Focus on Cardiac Safety**: Continuous ECG monitoring when preclinical data indicates risks to cardiac conduction, potentially avoiding later dedicated QT studies.
- **Monitoring Specific Reactions**:
  - Localised reactions are essential for topical drugs.
  - For defined AEs of interest (e.g., hepatic issues), detailed history (e.g., alcohol intake, medications) and tests for confounding causes improve attribution accuracy.

Determining MTD & AE Management in FIH Studies

- **Maximum Tolerated Dose (MTD)**:
  - Determined by **Dose-Limiting Toxicities (DLTs)** at preset severity levels.
  - Trials designed with stepwise dose escalation within cohorts or individuals.
  - Important to perform in the **intended patient population** to reflect disease-specific susceptibilities.
- **Safety Monitoring Plans**:
  - AE monitoring varies with predicted toxicity risk:
    - **Low-risk**: Sponsor-led monitoring.
    - **Moderate/high-risk**: Collaboration with independent experts or a data monitoring committee.
  - Independent monitoring is considered for placebo-controlled or high-toxicity risk trials.
  - **Plan Requirements**: Specifies data collection, review timelines, and criteria for dose adjustments or trial stopping based on toxicity signals.



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6. Biomarker assessment in FIH trials

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Biomarker Assessment in FIH Studies – Purpose & Planning

- **Role of Biomarkers**:
  - First chance to obtain biological readouts in humans, aiding **drug development** through target engagement and efficacy insights.
  - Supports **precision medicine** and diagnostic use (e.g., BRCA1/2 for cancer risk).
- **FIH Study as a Testing Ground**:
  - Confirms preclinical hypotheses, paving the way for **proof of concept (POC)** and clinical diagnostics.
  - Critical for oncology and other fields where biomarkers guide treatment and risk assessments.
- **Planning Biomarker Inclusion**:
  - Success relies on **thorough preparation**: literature review, bioanalytical method validation, clinical sampling strategy, and regulatory assessment.
  - **Fit-for-Purpose Compliance**: Defines the rigor of data handling based on biomarker role (e.g., POC vs. phase III support).

Biomarker Feasibility, Methods & Compliance

- **Method Development**:
  - Simple markers (e.g., serum proteins) vs. complex samples (e.g., tissue biopsies) need **validated methods** for accuracy.
  - Bioanalytical techniques vary by matrix: common assays (e.g., LC-MS) or custom methods may be needed.
- **Regulatory & Analytical Considerations**:
  - **Qualification vs. Validation**: Fully validated methods for phase III support; qualified assays suffice for early decisions.
  - **Data Analysis Standards**: Exploratory analyses may use simple methods, while advanced stages require **regulatory-compliant standards**.
- **Strategic Data Analysis**:
  - Prospective data plan (e.g., using normalization factors for variable matrices like urine) aligns rigor with clinical development goals.

Risk Mitigation Strategies in FIH Clinical Trials

- **Preclinical considerations**
- Understanding drug absorption, metabolism, and excretion to predict human exposure.
- Identify potential organ-specific toxicities and define the No-Observed-Adverse-Effect Level (NOAEL) in relevant animal models.
- Immunogenicity and Off-Target Effects Evaluating the potential for immune reactions, receptor cross-reactivity, and unexpected biological effects.
- Species Selection for Translation
- **2. Safe Dose Selection and Escalation Strategies**
    - Starting Dose Determination
    - Dose Escalation and Stopping Criteria:
    - Adaptive design with predefined dose increments.
    - Sentinels (small cohorts) dosed sequentially before expanding to larger groups.
    - Early stopping criteria for toxicity or unexpected adverse events

Risk Mitigation Strategies in FIH Clinical Trials

Clinical Site Preparedness

- Trials conducted in controlled hospital settings with rapid access to intensive care.
- Trained personnel to manage severe adverse reactions, including cytokine storms

- **Participant Selection**
  - Healthy volunteers or patients carefully screened for predisposing conditions.
  - Exclusion of individuals with high-risk genetic or immunologic profiles.
- **Real-Time Safety Monitoring**
  - Intensive monitoring in the first 24–48 hours post-dose.
  - Biomarker-driven safety assessments for early detection of toxicity.
  - Implementation of Data and Safety Monitoring Boards (DSMBs) for ongoing risk evaluation.
- **Ethical and Regulatory Safeguards**
  - Adherence to ICH E6 (GCP), ICH M3 (Nonclinical Safety Studies), and ICH S6 (Biologics)guidelines.
  - Informed Consent
  - Transparent risk communication to participants, detailing known and unknown risks.
  - Option for withdrawal at any stage without penalty.

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7. Analytical Considerations in FIH trials

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Statistical Considerations in Phase 1 Studies

Dose Escalation Strategy

Model-based designs (e.g., Bayesian adaptive designs) for optimal dose selection.

Stochastic Models: Account for variability in drug response across populations.

Sample Size Calculation

Small sample sizes (10-100 participants), but precision is critical for safety profiles.

Power Analysis

Ensuring sensitivity for detecting potential adverse effects at low doses.

Analysis of PK/PD Data

Non-compartmental analysis for estimating drug half-life, clearance, and volume of distribution.

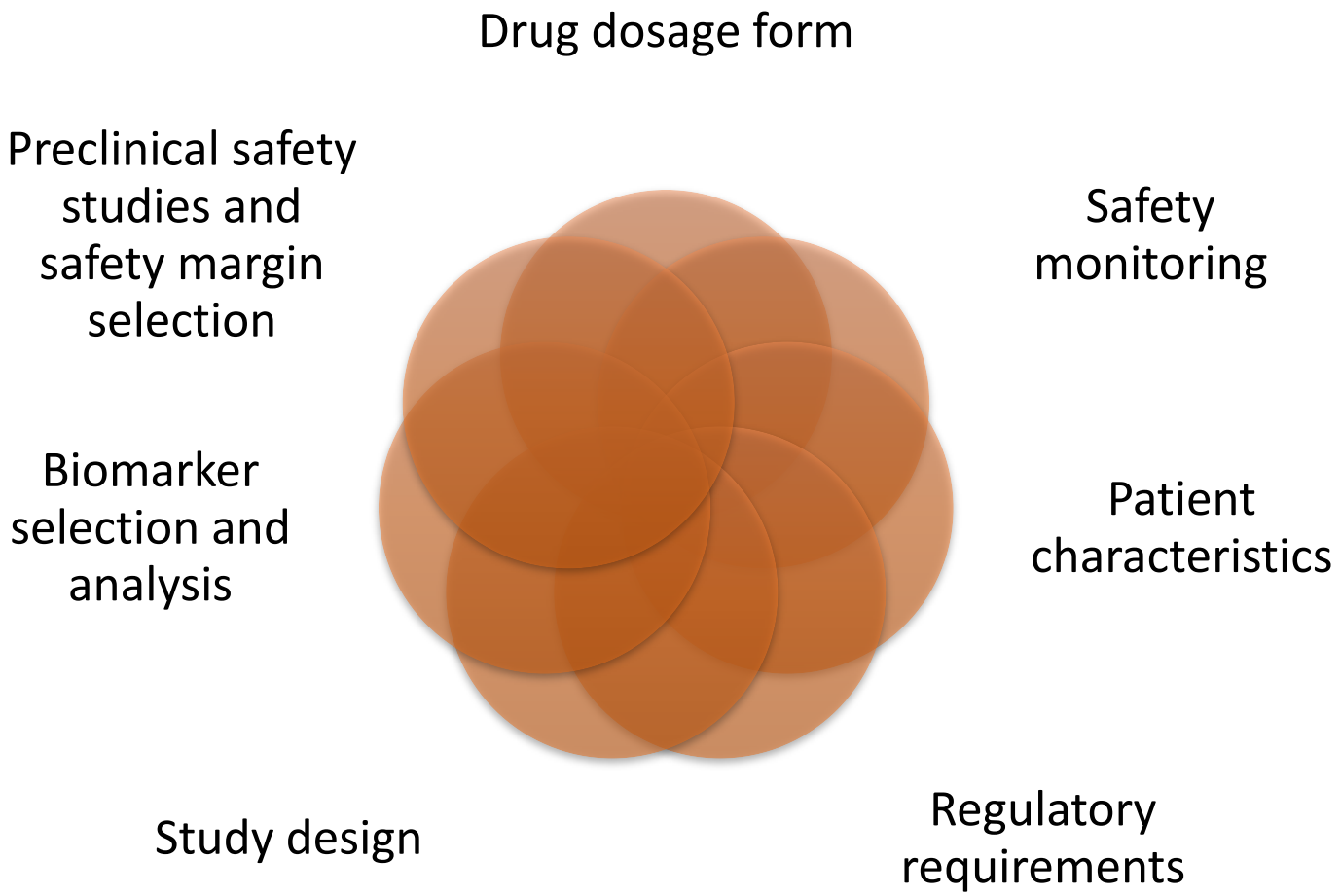
Statistical models

For dose-response relationships, with focus on linear vs. nonlinear kinetics.

Interpretation Challenges and Pitfalls in Phase 1 Studies

Safety data interpretation	• Adverse Events (AEs): Identifying causal links between drug and observed AEs. • Thresholds for Toxicity: Distinguishing between side effects and pharmacologically relevant toxicity.
Pharmacokinetic Variability	• Understanding inter-individual variability in drug absorption, distribution, metabolism, and excretion (ADME). • Impact of genetic polymorphisms on drug metabolism (CYP450, UGT, etc.).
Generalisation to Larger Populations	• Translating findings from healthy volunteers to patient populations. • Considerations for underlying diseases or drug interactions in later-phase trials.
Ethical Considerations:	• Balancing scientific goals with participant safety. • Regulatory oversight and informed consent processes.

Conclusion: Keep these in mind for your first in human trials



Thank you for listening

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