Drug Developers .....walk a fine line

Phases of Development

Drug Trials, Sharoon David; Preeti Patel; Peggy Y. Kim.

Preclinical Foundation prior to testing in Humans

Laboratory and animal studies support first-in-human testing:

Key questions:

Is there biological plausibility?

What is the toxicity profile? IC50 curves?

Early Pharmacokinetic/Pharmacodynamic models

What biomarkers or endpoints may be useful?

Toxicology package

Outputs inform the early Investigator's Brochure, Investigational New Drug application or equivalent regulatory submission.

Phase 1 trials

- Primary goal: evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics (will help inform the models built with pre-clinical data)
- Usually small participant numbers
- Often conducted in healthy volunteers, except for areas like oncology or high-risk therapies.
- Common designs:
  - Single ascending dose
  - Multiple ascending dose
  - Food-effect studies
  - Drug-interaction studies

<u>Key considerations:</u>

- Starting dose selection
- Dose-escalation rules
- Safety stopping criteria
- Staggered dosing
- Monitoring schedule
- Pharmacokinetic sampling
- Inclusion and exclusion criteria
- Safety review committee
- Keeping Health Agencies informed of safety events

XYZX2101

First-in-Human study design

Randomized, double-blind, placebo controlled single and multiple ascending dose study

Part 1: Single Ascending Dose

Cohort	Dose (mg)
I	10
II	30
III (Period 1: Fasted)	100
III (Period 2: Fed)	100
III (Period 3: PIB)	100
IV	300
V	600
VI	900

Part 2: Multiple Ascending Dose

Cohort	Dose (mg)
I	30 mg BID X 7 days
II	100 mg BID X 7 days
III	300 mg BID x 7 days
IV	500 mg BID X 7 days

Phase 2: Proof of concept and Dose refinement

- Primary goal: evaluate preliminary efficacy and further assess safety

- Often conducted in patients with the target condition

- Helps identify:
  - Effective dose range
  - Appropriate treatment duration
  - Candidate endpoints
  - Target population

- May be divided into:
  - Phase 2a: proof of concept
  - Phase 2b: dose-ranging and optimization

<u>Key Considerations:</u>

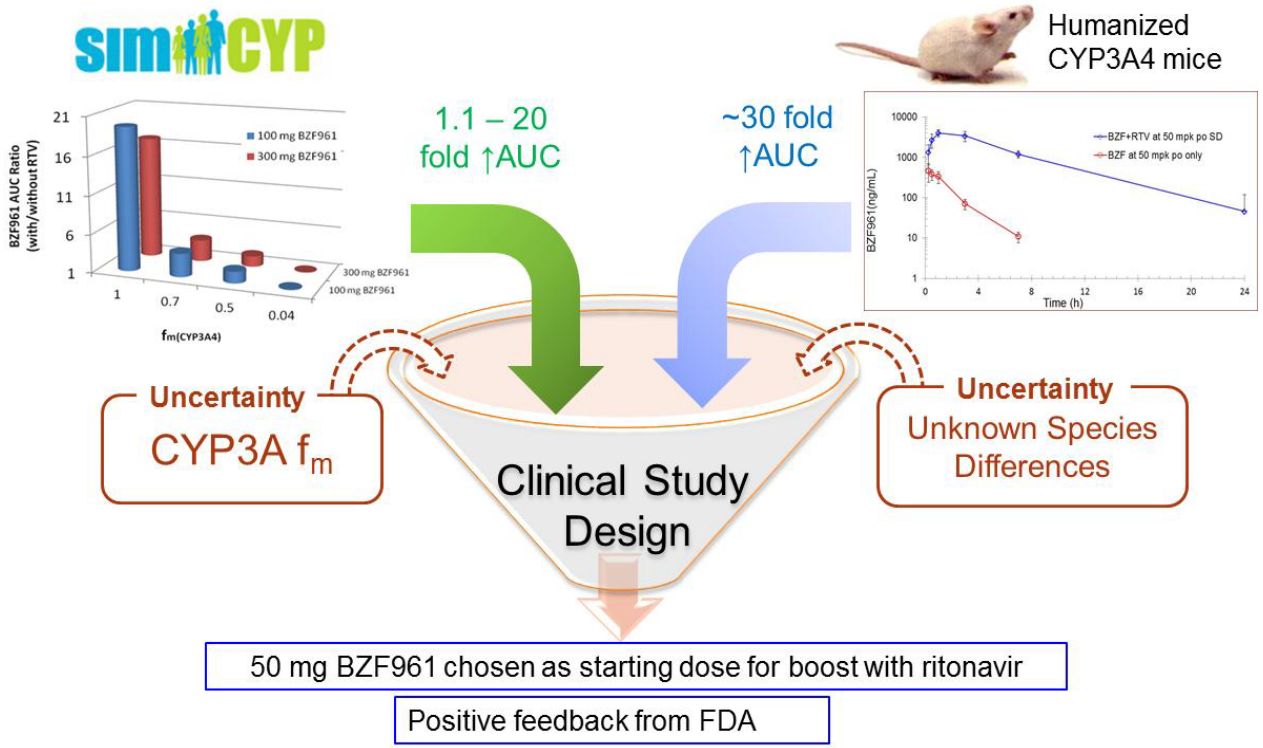
- Choosing clinically meaningful endpoints
- Defining responder criteria
- Selecting comparator or placebo control
- Determining sample size
- Balancing exploratory and confirmatory aims
- Planning interim analyses when appropriate
- Identifying biomarkers or subgroups

Example of seamless expansion

Background

- XYZ was a NS3/4 viral protease inhibitor
- First in human, healthy volunteer studies were ongoing
- Very high variability in exposure
- Clinical strategy to boost exposure with ritonavir
- XYZ is a sensitive substrate of CYP3A

What dose of XYZ should be administered with 100 mg bid ritonavir?



Impact

- 50 mg XYZ + 100 mg ritonavir bid was used as starting dose in patients
- A third patient cohort was added in the ongoing first in human healthy volunteer study

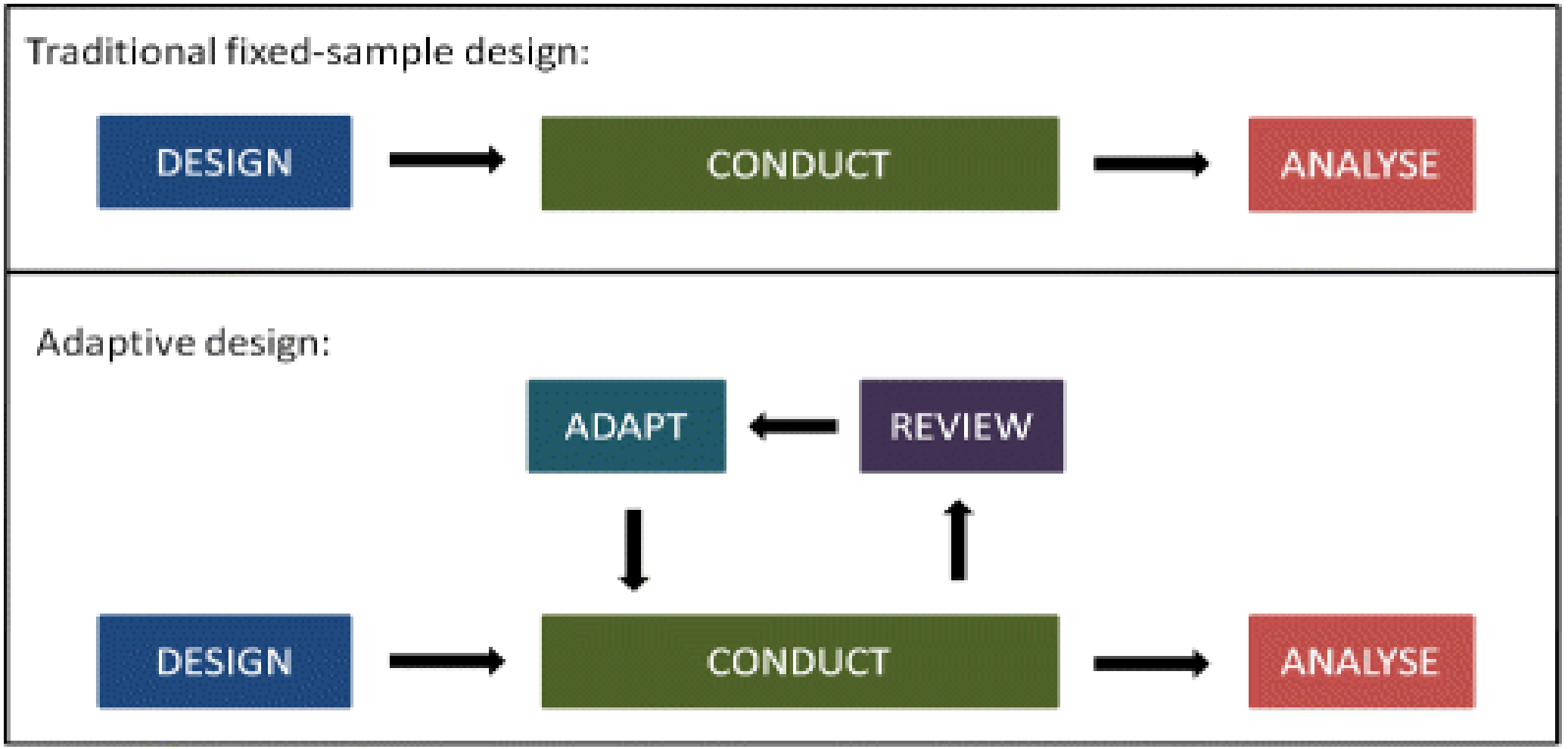
Phase 3: Confirmatory trials

- Primary goal: provide robust evidence for regulatory approval.
- Global, larger, more definitive studies.
- Usually randomized and controlled.
- Designed to confirm:
  - Clinical efficacy
  - Safety profile
  - Benefit-risk balance
  - Performance in the intended treatment population

Key points to consider:

- Clearly defined primary and secondary endpoints
- Adequate statistical power
- Randomization and blinding
- Comparator selection
- Multicenter feasibility
- Diversity and representativeness of participants
- Data monitoring committee
- Regulatory alignment before trial initiation

Adaptive clinical trials



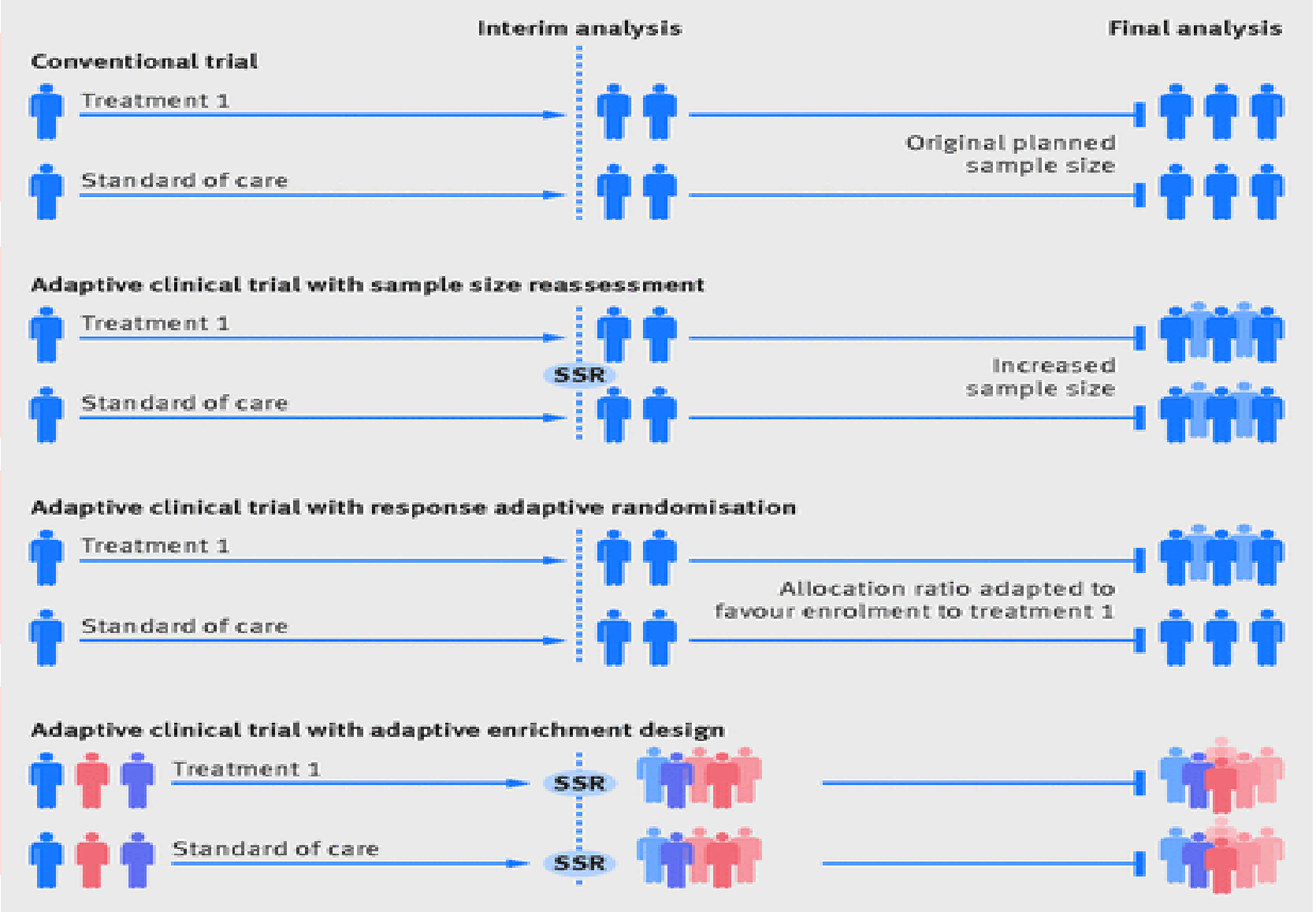
Advantages of adaptive designs

Interim analysis is not powered for key decision making

If interim analysis shows worse results than expected, the sample size can be reassessed and increased to ensure that the trial is adequately powered

If interim analysis shows promising results for a treatment, the allocation ratio can be modified to favors enrolment to that treatment

If interim analysis shows that a treatment has more promising results in one subgroup of patients, the study eligibility criteria can be modified to investigate the efficacy in subgroup



The “right” study for the “right” patient

Understand pain points from patients’ and caregiver’s perspective.

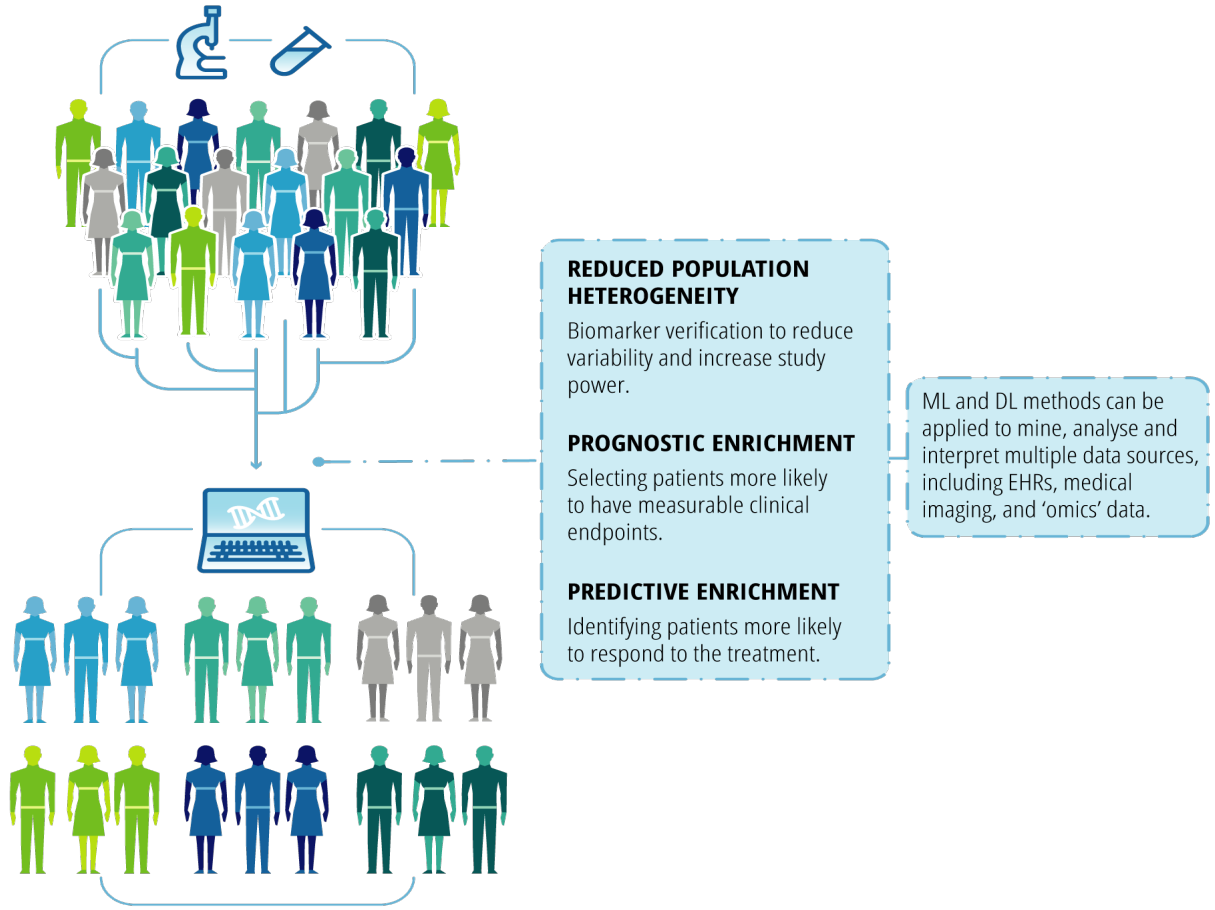
Social Media listening

HCP perspectives

FIGURE 3

How AI technologies can help deliver clinical trial enrichment strategies highlighted in FDA guidance

Trial enrichment strategies

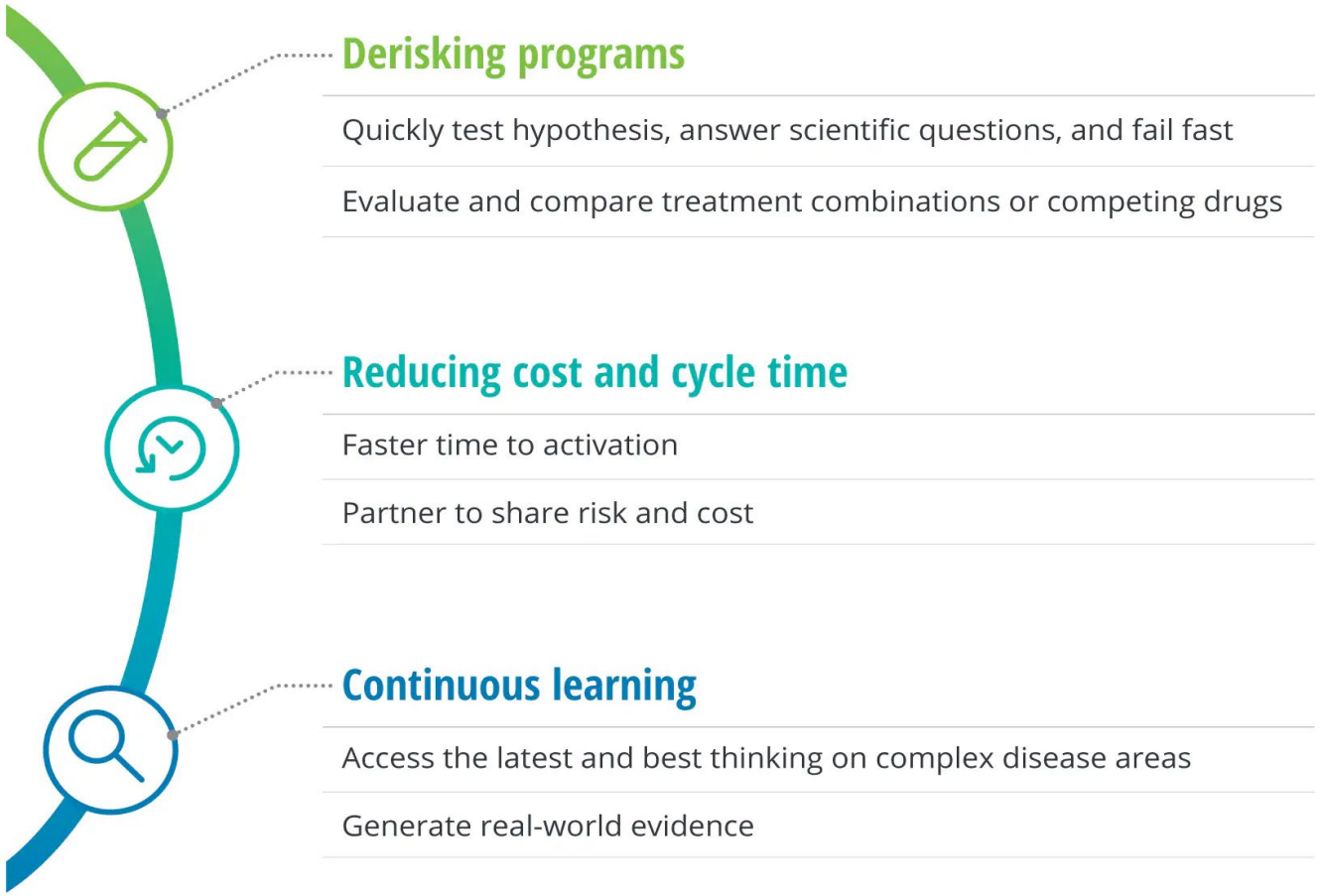


Source: Deloitte analysis.

AI in Clinical Trials, Deloitte report 2020

Master protocols

Type	Definition
Platform	A protocol employing multiple therapies for a single disease with therapies allowed to enter/exit on the basis of a decision algorithm
Basket	A protocol employing a targeted therapy for multiple diseases.
Umbrella	A protocol with more than one targeted therapy studied for a single disease



Master Protocols, Deloitte Insights

Example

Background

- An anti IgE was being developed for Chronic spontaneous urticaria
- 2 large global Phase 3 were ongoing
- Clinical strategy to initiate a clinical program in chronic inducible urticaria
- The overall prevalence of this disease is very low

Direct to Phase 3 strategy

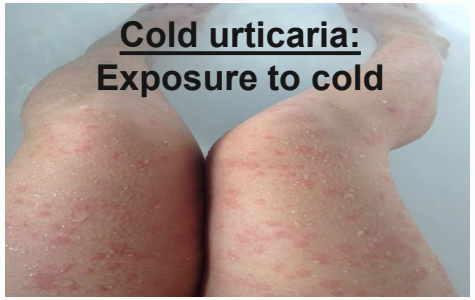
- A strong scientific rationale justifying common pathophysiology between chronic spontaneous urticaria and inducible uritcaria
- similar role of IgE
- Health Authorities granted a waiver for Phase 2 study.
- The planned Phase 3 in inducible urticaria to include adults but with a possibility to obtain label indication for adolescents and children

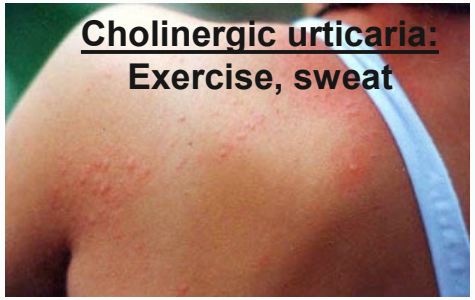
Patient Adboards and HCP surveys were conducted. Significant impact of disease on sleep, QoL and work

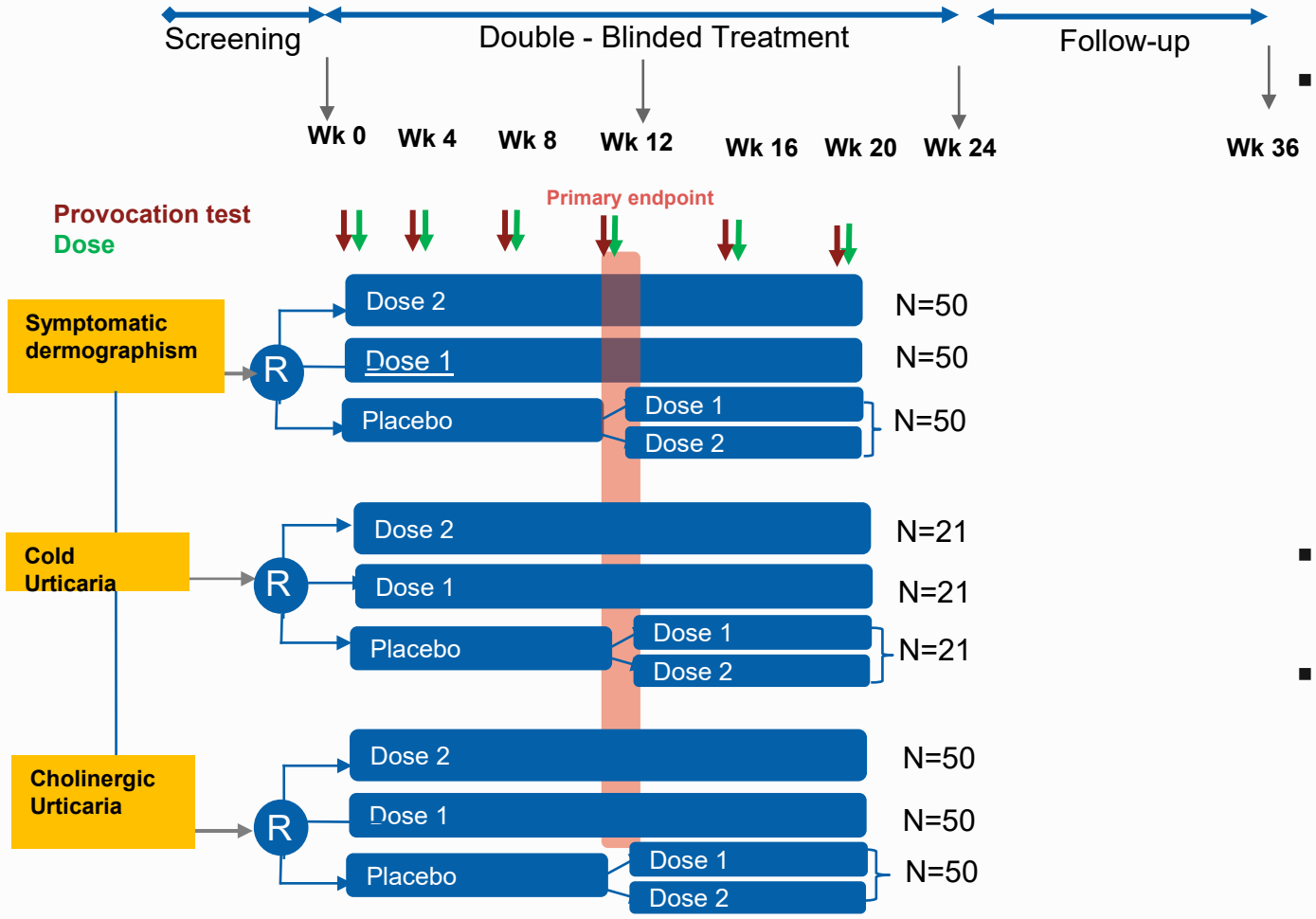
Clinical Study Design

- Itch was included as primary endpoint in the study
- Assessment of pain and burn were also included as endpoints

Basket study design to assess multiple CINDUs with common symptoms to enable a "inducible urticaria" indication in adults and adolescents







- Basket study design helps evaluate the efficacy of anti-IgE on three different subtypes of CINDUs.
  - Each subtype has an overall low prevalence
  - The 3 subtypes are closely related manifesting in similar symptoms
- The study allowed for dose selection within each subtype
- The testing strategy allowed for efficacy conclusions for each subtype while allowing pooling for safety.

Real world evidence

Refers to data and information gathered from a real-world setting

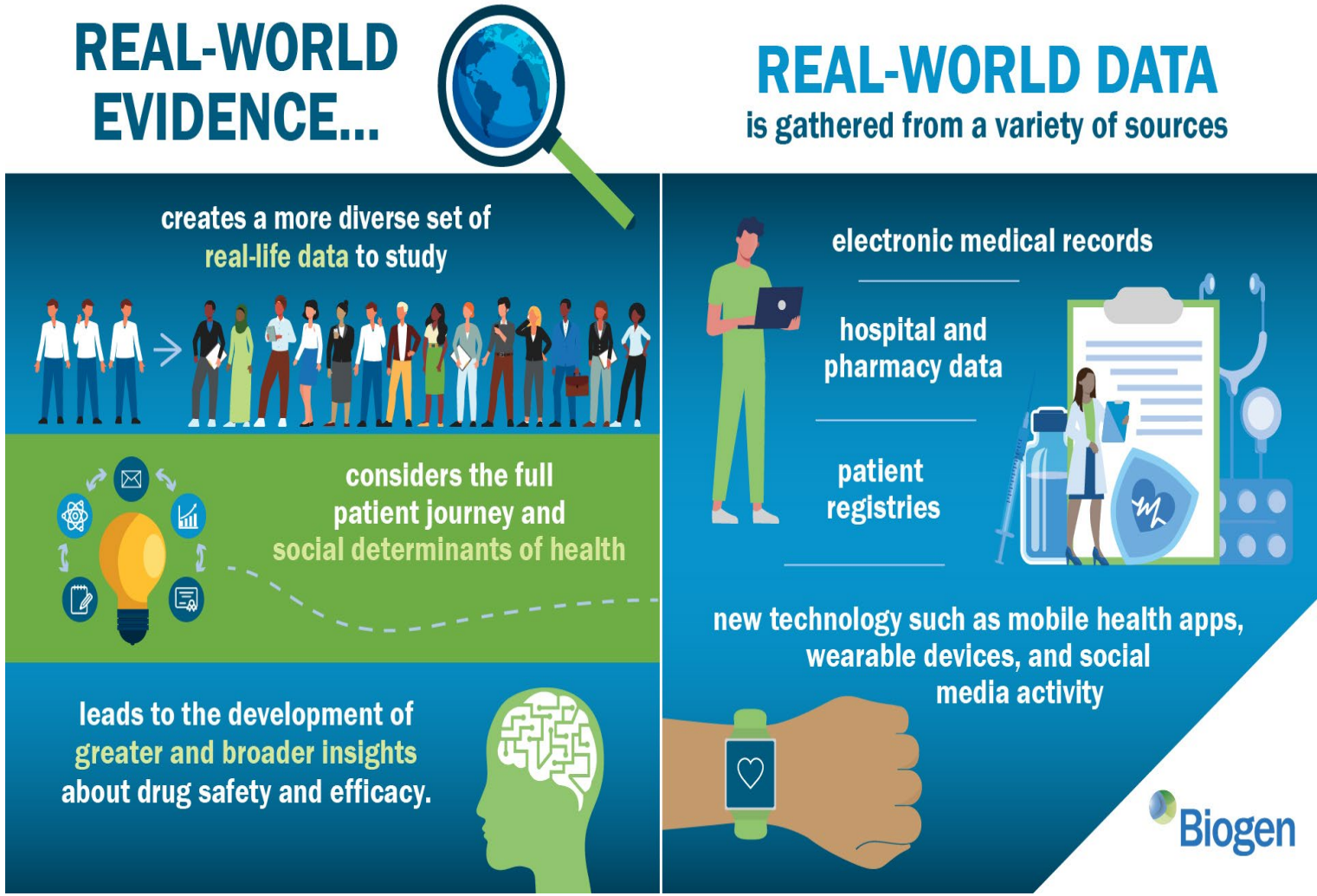
Data that are not being generated under controlled, clinical trial conditions.

Does not replace data from randomized clinical trials

Data from RCTs and RWE are complementary, not alternatives

Diverse data types

Data from disease registries, insurers' claims data, electronic medical records, observational studies



Example

Background

- **Cetuximab** is an epidermal growth factor receptor (EGFR) inhibitor with the following FDA-approved indications: colorectal cancer (CRC), metastatic, KRAS wild-type (without mutation), and squamous cell carcinoma of the head and neck (SCCHN)
- Previous approval was for **250 mg weekly dosing regimen**

RWE and Modeling strategy

- **Population pharmacokinetic (PK) modeling analyses** that compared the predicted exposures of cetuximab 500 mg Q2W to observed cetuximab exposures in patients who received cetuximab 250 mg weekly
- Pooled analyses of overall response rates, progression-free survival, and overall survival (OS) from published literature in patients with CRC and SCCHN, and OS analyses using **real-world data** in patients with mCRC who received either the weekly cetuximab or Q2W regimens

Results

- These exploratory analyses showed that the observed efficacy results were consistent across dosage regimens and supported the results of the population PK modeling analyses

Impact

- FDA approval and l**abel indication for a more convenient biweekly dosing regimen** (without generating data from an RCT)

FDA approves new dosing regimen for cetuximab | FDA

Caregiver survey to generate RWE to support discussions with payer

Questions	Purpose
• Occupation of the caregiver • Are you the primary income earner in the household • Average monthly income	Gives an insight into economic status of caregiver. Monthly income is a direct input parameter in the model
• Distance traveled to the site to obtain the reconstituted medication • Average time taken in traveling the distance to the site to obtain the reconstituted medication • Average time spent (including waiting period) at the site • Do you have to miss work when you visit the site to obtain the reconstituted medication (include partial days)	Provides data on how many workdays are missed
• Average out of pocket expenses incurred during travel to the site to obtain the reconstituted medication (include travel costs and food) • Average out of pocket expenses incurred due to boarding and lodging in case overnight stay is needed	Provides data on out-of-expenses incurred by caregiver

Ethical and Operational considerations

Ethical

- Informed consent
- Institutional review board or ethics committee approval
- Good Clinical Practice
- Participant safety monitoring
- Risk-benefit assessment

Operational

- Site selection and feasibility
- Recruitment and retention strategy
- Investigator training
- Study drug supply and accountability
- Data capture systems
- Monitoring plan
- Quality assurance
- Timeline and budget

Regulatory Considerations

- Align trial design with regulatory expectations
- Select clinically meaningful endpoints
- Justify dose, population, and comparator
- Use appropriate statistical methods
- Maintain data quality and integrity
- Plan safety monitoring and adverse event reporting
- Register trials and report results transparently
- Consider regional requirements for global studies
- Design studies to support the intended product label

Regulatory interactions and Special Population Plans

- Early and frequent communication with regulators can reduce development risk.

- Common interactions may include:
  - Pre-IND meeting
  - Scientific advice meeting
  - End-of-Phase 2 meeting
  - Type B or Type C meetings with FDA
  - Protocol assistance for orphan products
  - Special protocol assessment in some cases

- These meetings can help confirm whether the proposed design, endpoints, and analysis plan are likely to support approval

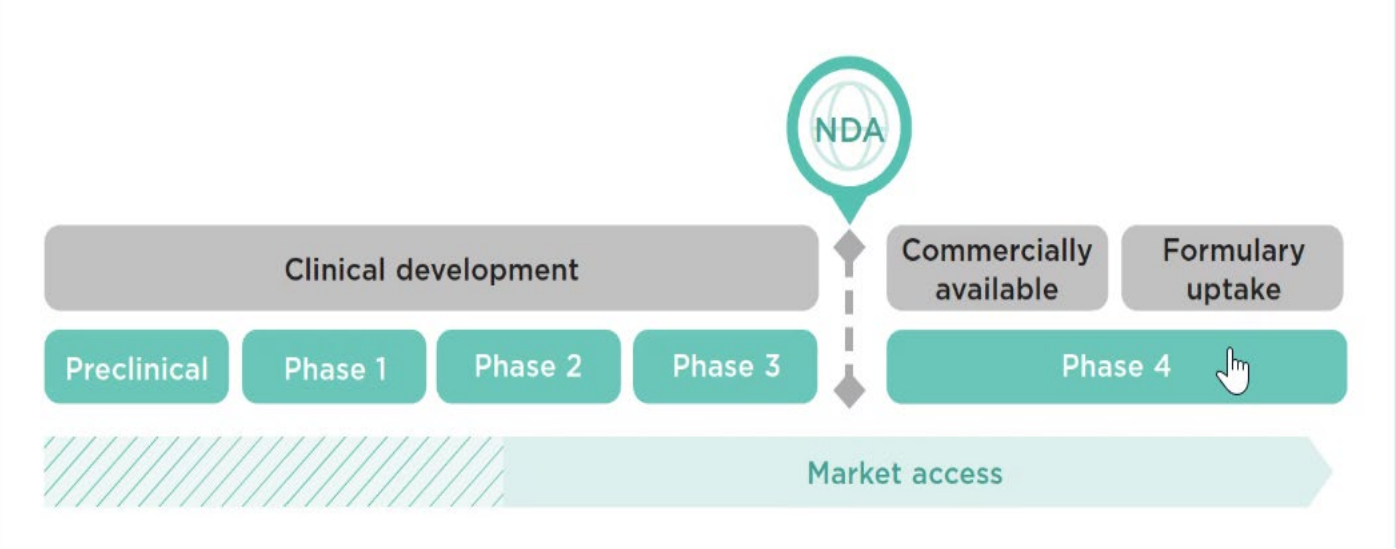
- Depending on the product and indication, regulators may require plans for special populations.

- Examples: Pediatric study plans, Geriatric studies, Renal impairment studies, Hepatic impairment studies Drug-drug interaction studies, Pregnancy and lactation considerations

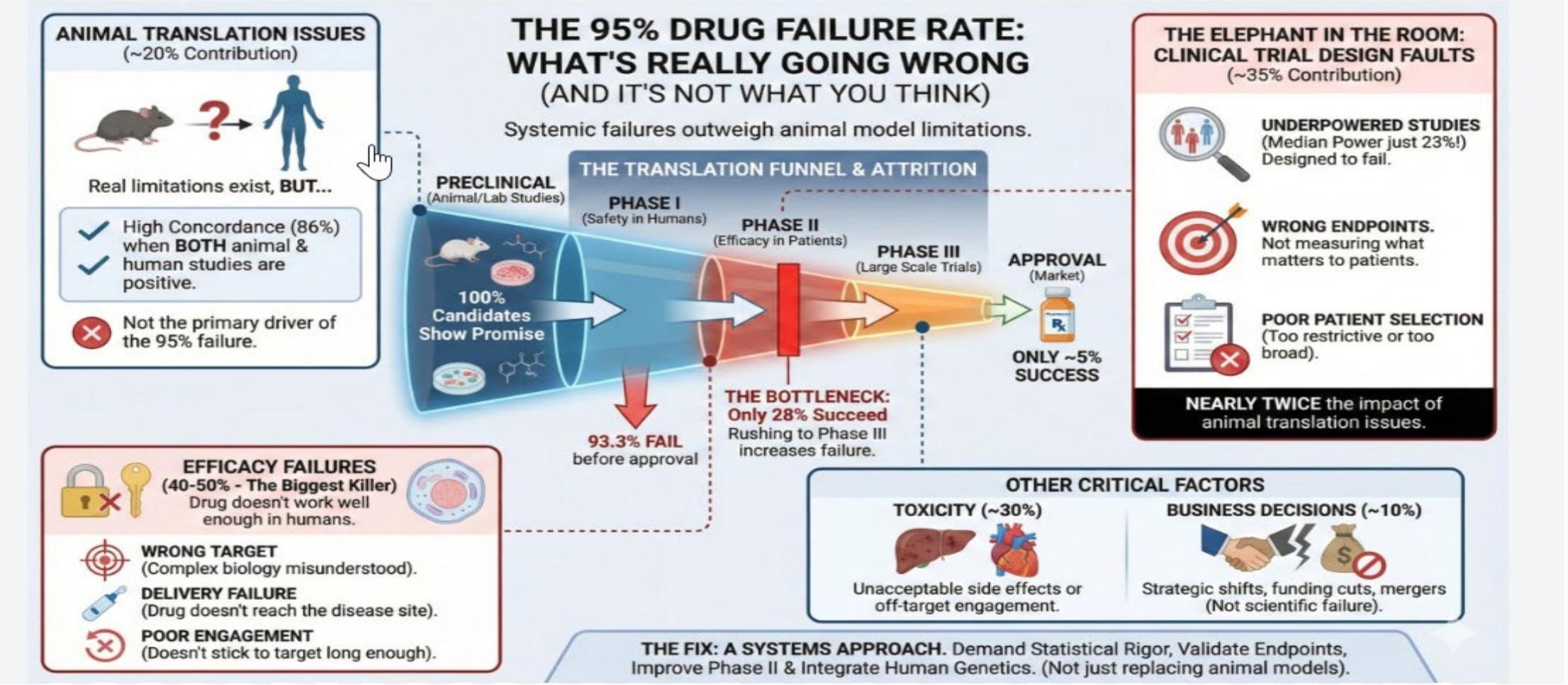
Integrated Development Plan

- Clinical trial planning should not be phase-by-phase in isolation. Each phase should answer questions needed for the next phase.

- A good development plan integrates:
  - Scientific rationale
  - Nonclinical evidence
  - Clinical pharmacology
  - Regulatory strategy
  - Statistical strategy
  - Commercial and patient-access considerations
  - Post-marketing evidence needs



Despite best planning and efforts, some trials fail



Future of Science article by Stefano Gaburro, PhD. **The 95% Drug Failure Rate: What's Really Going Wrong (And It's Not What You Think)**