In silico clinical trials: the future of biomedical product testing

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Drug Product cycle

Target

- Needs identified
- Target identified
- Hits identified
- Leads identified

Design

- Leads optimized
- Candidate confirmed
- Preclinical development
- Start Prenomination
- Phase IV
- Phase IIIb
- Phase IIIa
- Phase IIb
- Phase IIa
- Phase I
- First time in Man

Efficacy

- Proof of Principle
- Proof of Concept
- Phase III results

Risk

- Phase I

Assessment

- Launch
- Postmarket analysis

- Target identified
- Hits identified
- Leads identified
Cost to Develop New Drug Now Exceeds $2.5b

Source: Tufts Center for the Study of Drug Development, USA - 2014
Drug Discovery and Development: A LONG, RISKY ROAD

PRE-DISCOVERY

5,000 - 10,000 COMPOUNDS
3 - 6 YEARS

DRUG DISCOVERY

250

CLINICAL TRIALS

PHASE 1: 20 - 80
PHASE 2: 100 - 300
PHASE 3: 1,000 - 3,000
6 - 7 YEARS

IND SUBMITTED

FDA REVIEW

LG-SCALE MFG

0.5 - 2 YEARS

ONE FDA-APPROVED DRUG

PHASE 4: POST-MARKETING SURVEILLANCE

Source: Pharmaceutical Research and Manufacturers of America
When does it fail?

Rates of success for compounds entering first in man that progress to subsequent phase

- 70% of oncology drugs that enter Phase 2 fail to enter Phase 3
- 59% of oncology drugs that enter Phase 3 fail
- Late stage failure leads to enormous risk
- Failure is primarily due to lack of efficacy > toxicity

Kola & Landis; Nature Reviews Drug Discovery 2004
Why does it fail?

PWC identifies 7 major trends:

- The burden of chronic disease is soaring.
- Healthcare policy-makers and payers are increasingly mandating what doctors can prescribe.
- Pay-for-performance is on the rise.
- The boundaries between different forms of healthcare are blurring.
- The markets of the developing world, where demand for medicines is likely to grow most rapidly over the next 12 years, are highly varied.
- Many governments are beginning to focus on prevention rather than treatment, although they are not yet investing very much in pre-emptive measures.
- The regulators are becoming more risk-averse.

Recommendation: “Greater use of new technologies to “virtualise” the research process and accelerate clinical development”
2005 – 2015: ten years of VPH

2005: the VPH is born

2007: STEP

2008: FDA approves Kovatchev-Cobelli diabetes simulator to replace animal experimentation (1979)

2010: VPH Institute

2012: Insigneo

2014: FDA allows marketing of HeartFlow vFFR-CT software (1998)

Use of *in silico* in medical device

- Medical devices companies use computer modelling & simulation extensively
- But not in the pre-clinical and clinical phases

*Results adapted from 2014 MDIC survey of 35 participating medical device companies*
A Strategy for *in silico* Clinical Trials

The University Of Sheffield.

VPH Institute

Obsidian

Lynkeus
Why Avicenna?

• Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn Al-Hasan ibn Ali ibn Sīnā
• The Canon of Medicine
  – The drug must be free from any extraneous accidental quality.
  – It must be used on a simple, not a composite, disease.
  – The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
  – The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
  – The time of action must be observed, so that essence and accident are not confused.
  – The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
  – The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.

990 years!!!
Foundation: where we started from

- We do not know who we are
- We do not know what we do
- We do not know what we need
- We do not know how to assess
- Potential is wasted
- The world is not ready
Goals: where do we want to go

Community of Practice

Roadmap

Industrial Alliance
The Avicenna Community of Practice

Experts

Event 1 | Event 2 | Event 3 | Event 4
-------|--------|--------|-------
100    | 200    | 400    | 500   

[Logos and logos of the University of Sheffield, VPH Institute, OBSIRIAN, LYNKEUS, INSIGNEO, and the European Union.]
Distribution of Avicenna experts

% composition expert clusters

- Research: 31%
- Providers: 28%
- Producers: 21%
- Regulatory: 15%
- Others: 6%

Providers

- Large Biopharma: 58%
- Medical Devices: 22%
- Small Biopharma: 8%
In silico clinical trials

The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention.
Individualised model?

- Prediction
- Observation

The prediction is a member of the population

The prediction is near the average of the population

The prediction is near to individual observation

A model is individualised depending on how its challenged.
The 3 R

- **Reduce**: reduce the number of subjects involved in a trial, or its duration

- **Refine**: decrease the discomfort for the subjects the trial involves

- **Replace**: run entire portions of a clinical trial *in silico* rather than *in vivo*
Two ethical balances

Animal welfare

Human welfare

Collective Benefit

Individual Discomfort

Animal welfare

Human welfare

Collective Benefit

Individual Discomfort

Animal welfare

Human welfare

Collective Benefit

Individual Discomfort
The 3 R - modified

• Maximise the usefulness of pre-clinical trials on animals

• Reduce: reduce the number of subjects involved in a trial, or its duration

• Refine: decrease the discomfort for the subjects the trial involves while increasing the potential collective benefits

• Replace: run entire portions of a clinical trial *in silico* rather than *in vivo*
Animal experimentation: in silico 3R

mouse

tibia
Changes in bone strength

Tibia Strength [BW]

Mouse age [weeks]
CT-based SSM predict risk of hip fracture with 80-85% accuracy in retrospective clinical trials
Juvenile Idiopathic Arthritis

Healthy knee

Affected knee
Develop patient-specific whole body musculoskeletal dynamics model

The Physiological Envelope, the deployment envelope

- The entire range of possible values a physiological parameter can assume in a given subject is referred as the “physiological envelope” (Viceconti et al., 2015)

- Reliably estimate the physiological envelope for a number of physiological parameters relevant to the design of specific families of biomedical products

- Quantification of the reproducibility of the deployment/implantation of specific classes of biomedical products
Reducing, refining, and partially replacing clinical trials

• ISCT models to predict very long-term outcomes, and under-selected (unusual) populations

• Patient-specific models to refine the clinical outcome quantification

• Models to provide reliable surrogate metrics for endpoints to shorten the clinical trial

• In silico cohort to augment clinical cohort using Bayesian trial design
From validation to confidence

• Medicine is to decide about an individual based on his/her being “similar” to idealised target cohort.

• Personalised medicine is about making this idealised target cohort smaller.

• If the observational values (measurements) are affected by uncertainty much smaller than our predictions:
  – The input parameters define the target cohort
  – The individualisation level define our predictive ambition
  – The Predictive accuracy define the confidence
Thank You!

INSGNEO
Institute for in silico Medicine

The University Of Sheffield.
Sheffield Teaching Hospitals
NHS Foundation Trust

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