In silico clinical trials: The Avicenna Roadmap

Marco Viceconti
Avicenna Support Action, Coordinator
2015 BMES-FDA Frontiers in Medical Devices Conference
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.

1025  990 years!!!  2015
In silico clinical trials

• **In silico clinical trials**: the use of computer simulation in the development and in the assessment of new drugs, new medical devices, new health technologies.

• **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.
A model is individualised depending on how its challenged.

- **Prediction**
  - The prediction is a member of the population.
  - The prediction is near the average of the population.
  - The prediction is near to individual observation.

- **Observation**

---

**Graphs:**

- **Observations vs. Cases**
- **Frequencies**
- **Predictions vs. Observations**
Industrial sectors - Today

- Medical devices
- Biotech products
- Pharma

Research Hospitals ➔ CROs ➔ Regulatory
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
Building the Community of Practice
The engagement process

- Mapping the territory
- Stakeholders identification
- Contacts establishment
- Awareness building
- Contribution mechanism
Building awareness

• Creation and distribution of informative material
  – sent invitation emails with an opt-out mechanism

• Creation of a public website
  – http://avicenna-isct.org/

• Creation of a LinkedIn discussion group
  – anyone can join and contribute

• Production of e-news re-distributed via the VPH institute website and newsletter
  – over 8000 unique contacts

• Dissemination through consortium presentation at conferences of reference
Contribution mechanism

- Participation to Alignment Optimisation Cycles
- Participation to Avicenna events
- Discussions on the LinkedIn forum
- Roadmap drafting
The Avicenna Community of Practice

Experts

Event 1  Event 2  Event 3  Event 4

0  100  200  300  400  500  600
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
LinkedIn Avicenna group

- 229 members to date
- To join: http://tinyurl.com/avicenna-linkedln
Consensus process
# The Avicenna Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Title</th>
<th>Location</th>
<th>No. of attendees</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trajectory, Staging and Goals</td>
<td>Rome, Italy</td>
<td>35</td>
<td>20th-21st March 2014</td>
</tr>
<tr>
<td>2</td>
<td>Industrial Research Participation</td>
<td>Rome, Italy</td>
<td>50</td>
<td>5th-6th June 2014</td>
</tr>
<tr>
<td>3</td>
<td>Research Challenges</td>
<td>Lyon, France</td>
<td>50</td>
<td>30th-31st October 2014</td>
</tr>
<tr>
<td>4</td>
<td>Component Development</td>
<td>Brussels, Belgium</td>
<td>50</td>
<td>19th-20th February 2015</td>
</tr>
<tr>
<td>5</td>
<td>Strategy for continuation</td>
<td>Barcelona, Spain</td>
<td>&gt; 100</td>
<td>4th-5th June 2015</td>
</tr>
</tbody>
</table>
In Silico Clinical Trials: the future is now

Hosted by AQuAS
Agency for Health Quality and Assessment of Catalonia
4th and 5th June 2015, Barcelona, Spain
Avicenna Event 1-4 Format

Social Programme:
- Cultural excursion
- Social dinner

Presentations:
- From Avicenna Team
- From ISCT Experts

Discussion:
- In plenary
- In break out groups
- Voting system
Alignment Optimisation: What is it?

Measure
Discuss what we could do.

Maximize
Agree what we will do.

Maintain
Change what we’re doing?

http://www.schellingpoint.com

© SchellingPoint 2015
Roadmap
Roadmap: writing progress

Words

<table>
<thead>
<tr>
<th>Version</th>
<th>Words</th>
</tr>
</thead>
<tbody>
<tr>
<td>version 1</td>
<td>0</td>
</tr>
<tr>
<td>version 2</td>
<td>10000</td>
</tr>
<tr>
<td>version 3</td>
<td>20000</td>
</tr>
<tr>
<td>final draft</td>
<td>50000</td>
</tr>
</tbody>
</table>

The final draft contains 50,000 words.
The process

1. Run an Alignment Optimisation Cycle
2. Collaboratively write draft roadmap
3. Send to Editors, incorporate revisions
4. Send to all experts 2wks before event
5. Collect written and oral comments
6. Collect event outputs
Editorial team

• Pen holders: MV, EMF, AH
• 29 authors
• Over 200 reviewers
• 216 request for changes last revision
In Silico Clinical Trials: How Computer Simulation Will Transform The Biomedical Industry

An international research and development roadmap for an industry-driven initiative

I. A layperson’s introduction
II. Avicenna roadmap: motivation and process
III. The industrial need for in silico clinical trials
IV. The socioeconomic need for in silico clinical trials
V. Use cases for medical devices
VI. Use cases for pharmaceuticals
VII. Horizontal challenges and emerging technologies
VIII. Research challenges related to medical devices and combined products
IX. Research challenges related to pharmaceuticals and biotech products
X. The Avicenna Alliance
XI. Conclusions
The challenges (medical devices)

A. Beyond validation: model credibility

B. In silico design and pre-clinical assessment of wearable or implantable devices

C. Automate ISCT for medical devices

D. Visual analytics to explore high-throughput simulation results

E. The Physiological Envelope, the deployment envelope

F. Reducing, refining, and partially replacing clinical trials
Model credibility

• Avicenna supports the concept of model credibility, and refers to the work of ASME V&V-40 committee

• Validation target:
  – Aim for any member of the population
  – Aim for the average of the population
  – Aim for each member of the population

• The risk of tuneable inputs:
  – Dim(validation output) >> Dim (Tuneable Inputs)
Design and pre-clinical assessment

- Development of modelling techniques for all clinically reported failure modes
- Retrospective application to designs widely tested in the clinics to build confidence
- Run in parallel and in double blind in silico and experimental evaluations of new designs
- When clinical adverse effect is not clearly associated to engineering failure use ISCT to test if the proposed failure of the device could actually produce the effects observed clinically
Automate ISCT

- High-throughput: fully automated 2 hours process → 4320 cases x year
- Statistical atlases of model anatomo-physical population variability (models on their own, need validation)
- Device deployment models, to automate the surgical simulation, provide statistics on anatomical fitting on new designs
- Support for “replay” technologies, where whole in silico trial can be automatically repeated after minor modifications are made to the device
Visual analytics to explore high-throughput simulation results

• For each design thousands of simulation results: now what?

• Information & scientific visualisation technologies that allow rapid comparison of multiple simulation cases in meaningful ways

• Interactive visualisation technologies that facilitate communication with non-technical members of the design team, such as clinical specialists, or regulators
The Physiological Envelope, the deployment envelope

• How will the patient treat my device?

• 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 medical devices

• Quantification of the reproducibility of the deployment/implantation of specific classes of medical devices
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
- Replication of real clinical trials to demonstrate models credibility
Get involved

- Join the community of practice
  - Write to info@avicenna-isct.org

- Join Avicenna-ISCT LinkedIn Group
  - http://tinyurl.com/avicenna-linkedindin

- Revise and comment Roadmap final draft
  - http://avicenna-isct.org/roadmap/
  - Available from May 26th, 2015