INSIST Industry Focus Group Discussions at INSIST All hands workshop Rotterdam – a Whitepaper

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Abstract

In silico clinical trials hold the promise to use computational techniques to support and accelerate the evaluation and introduction of new medical products at reduced costs. The INSIST (In silico clinical trials for treatment of ischemic stroke) initiative has been set up to develop an in silico platform for the simulation and evaluation of novel treatments for acute ischemic stroke. INSIST comprises the generation of virtual populations representing stroke patients, the in silico modeling of thrombosis, thrombolysis, and thrombectomy and of brain tissue death due to the lack of oxygen, and an estimation of clinical relevant endpoints. The

combination allows the in silico simulation of clinical trials. Part of the INSIST initiative are Focus Group Discussions involving specific stakeholders and contributors. Following a Clinical Focus Group Discussion in April 2019, we organized an Industry Focus group meeting in November 2019. Purpose of this meeting was to inform interested companies producing and marketing stroke-related devices and drugs on our work and to obtain feedback on our approaches and advice on our future plans.

Introduction

Computer modelling plays an increasingly important role in research and development of biomedical products. In silico models hold the promise that, in combination with patient models that accurately represent important patient characteristics, they can be used to set up in silico clinical trials in which "virtual" patients are exposed to "virtual" treatments. In silico clinical trials can potentially reduce, refine, and partially replace human clinical trials. With the advent of new stroke treatments, new trials are being planned. Because in silico modelling allows early and fast hypothesis testing and supports trial design, the next generation clinical stroke trials can greatly benefit from in silico clinical stroke trials. This holds the promise that in silico models enable enhanced efficacy, cost reduction, and speed up the introduction of new therapies, devices, and medication for acute ischemic stroke. With INSIST, we will advance in silico clinical trial methods in the field of acute ischemic stroke by simulating randomized controlled trials for novel acute ischemic stroke treatments.

The main goal of INSIST is to realize in silico clinical stroke trials for devices and drugs designed for treatment of acute ischemic stroke. Such an in silico clinical ischemic stroke trial consists of the generation of a population of virtual stroke patients, an in silico model of treatment, and an in silico model of the biophysiological aspects of the human response to stroke.

Focus group discussions involving specific stakeholders and contributors are part of the INSIST project. During these discussions the concept of INSIST is presented and opportunities with stakeholders are discussed.

The INSIST Focus group concept goes beyond the communication of the results to our stakeholders at large. Indeed, the Focus group concept is also a tool to develop exploitation strategies. The Focus group discussions also assure involvement of parties that have expressed partnering interest to provide a platform of exchange with the Technology Transfer Panel and the members of the Advisory Board.

The Focus group discussions address exploitation opportunities and refinement of the implementation of *in silico* clinical stroke trials. The Focus group discussions aim to enhance re-use of INSIST results and potential further collaboration beyond the end of the project.

A first Focus Group, organized in Milan on April 4-5, 2019, specifically addressed clinicians as important stakeholders in our research[1]. During that meeting we concluded that the concept of in silico stroke trials was considered promising. Especially the thrombectomy modeling was regarded valuable. The modeling of tissue death and its effect on clinical outcome was considered the most complex and risky.

[1] https://www.insist-h2020.eu/index.php/dissemination/output/68-insist-clinical-focus-groiup-white-paper

This second meeting considered the view of the industrial stakeholders. During our all hands meeting on November 11-12, 2019 in Rotterdam, we organized a discussion with representatives of key companies marketing devices and drugs with (possible) relevance for diagnosis and treatment of acute ischemic stroke. This white paper reports on the setup of the discussion, the perception that these stakeholders have on the INSIST work, the critical points in improving health care in acute ischemic stroke and the suggestions for detailing and fine-tuning of the INSIST work and future work based on in silico methods.

Methods

Setup of the discussion

Relevant stakeholders for this discussion were defined as companies with an interest in stroke treatment and production of devices or drugs, as well as with a regulatory interest, and the executive team of INSIST. A preliminary version of this report was distributed among participants with the request to provide further written input, which was then included in the final report. We started with a brief explanation of the INSIST goals and organization, followed by a discussion on a number of points as listed below.

Points for discussion

The following topics were selected for discussion.

1. *What does it take for in silico RCT's to make a next step;*
2. *Weak spots and valuable aspects;*
3. *How to strengthen collaboration with regulatory bodies;*
4. *Business opportunities;*
5. *Further collaboration during and beyond end of the project;*

Implementation of the discussion

The meeting was organized in two parts. In part A (2 hours), a short general introduction to the project was given by CM and AH, followed by a 15 minutes introduction of 7 companies. In part B, a 2 hours round table was organized between the representatives of these companies, a business developer (MM at AMC), the INSIST management team (CM, AH, HM, EvB, LJ) and three additional INSIST WP leaders (PMcG, AvdL, FR).

INSIST Industry Focus Group Discussions

What does it take for in silico RCT's to make a next step?

Three possible in silico clinical trials were discussed, asking which one would be most interesting and what should be the next step. These potential trials were:

1. Simulating the ongoing MRCLEAN NO-IV trial (https://mrclean-noiv.nl/)
2. Simulating a new thrombectomy device
3. Simulate a different population (e.g. patients of a different age)

Many agreed that the first suggestion would probably be the most interesting, because it allows direct validation against the trial results. Related to this trial, the INSIST consortium asked the industrial partners whether in silico trials would be an interesting tool for evaluation of specific pharmaceutical components before going into clinical trials. This was certainly considered to have its value. For example, the use of thrombolytic drugs before or after thrombectomy (in case the thrombus could not be removed completely) is a scenario that could very well be addressed by in silico methods. Yet, a concern of simulating pharmaceutical versus device trials is that the drug effects depend on complex and unknown biology rather than well-defined mechanical laws.

As concerns the next steps, a further discussion ensued on the current state and possibilities of INSIST: what can be modelled? Is it possible to model the end-points of clinical trials? In terms of "maturation" how far is the INSIST project? Beyond the technical development, DV argued that pharmaceutical companies need to embrace and invest into these concepts.

Several industrial partners wondered whether INSIST tries to simulate the execution of clinical trials in order to optimize them. We explained that the current goal of simulating the MRCLEAN NO-IV trial is to validate our approach, but clearly that future in silico clinical trials indeed aim to select promising trials and optimize trial design, leading to e.g. less needed patients. The general consensus is that we will never completely ban "normal clinical trials".

The question was raised whether INSIST aims to come to a patient approach rather than a population approach. We agreed that a specific patient approach (i.e. the use of an 'INSIST' model for decision making in specific cases) might be too optimistic or even infeasible now. INSIST is not designed for this. Rather, we hope that in silico trials might replace clinical trials in testing specific scenarios.

Weak spots and valuable aspects

Diana Demet Tangun (Vesalio) points out that there are two main challenges:

Firstly, there is a technical challenge: every year new devices come out, so the risk exists that by the time the INSIST project is finished, there might be new technologies out there that we cannot model yet.

In response the team from INSIST discussed the modular nature of the work. Several crucial modules are independent of such developments. These include the virtual population model and the tissue model for infarct progression. Moreover, INSIST aims to be a proof of concept on how to do these in silico clinical trials. For that reason, possible technical developments are less relevant. Moreover, we anticipate that in the future the in silico clinical trials and underlying modeling approaches are not lagging technical developments but rather leading them.

A second challenge is that we have to take into account that the definition of success is changing: success is not about solving intellectual challenges, but about a patient being able to go to the toilet without help. More formally: can we really provide good predictions of the distribution of modified Ranking Scales in trial outcomes?

We indicated that the purpose of in silico clinical trials is not to completely replace real trials, but to select such trials and optimize their design. How well this will help has to be

demonstrated in future work. To draw a parallel: the early thrombolysis trial failed[1-3]. But there were some people at Boehringer Ingelheim (Thierry Danais) who never gave up and finally made it work. So, even though the industrial stakeholders believe that we are on a bumpy road, they indicate that this is a very valuable road to go and that we should not give up too easily.

How to strengthen collaboration with regulatory bodies

In silico clinical trials form a completely new approach, requiring a change of both attitude among stakeholders and adaptation of formal regulations before marketing can become realistic. We agreed that improving attitude towards in silico clinical trials in general and particularly INSIST requires continuous efforts in explaining and clarifying the concept and demonstrating feasibility to our stakeholders. We need to further define the opinion leaders here and approach them.

The FDA is embracing in silico clinical trials in the USA. Notably Tina Morisson at FDA is driving this progress. In silico clinical trials also have the interest of the EMA. Indeed, INSIST representatives recently met with experts on regulatory issues for informal discussions concerning a validation plan. However, a European notified body for assessing the conformity of in silico clinical trial approach still has to be identified or set up. This issue was also addressed in a meeting during the recent ComBiomed conference with the other in silico clinical trial projects, chaired by Marco Viceconti (University of Bologna). It is clear that further meetings of the project leaders with the regulatory bodies and also the stakeholders are required in order to establish progress on this issue.

Business opportunities

INSIST is designed as a demonstration project, and the Technology Readiness Levels of the final in silico clinical trials are planned to be low. Therefore, this ‘end product’ is not expected to generate immediate business opportunities. Yet, several parts of the work, notably the modeling of thrombectomy devices, may generate business opportunities for device companies who could use our methods and results for stent design. It will be crucial to continue INSIST after the formal end date in order to optimize such opportunities and work towards further introduction of in silico clinical trials as an important step in development of new procedures, devices and drugs in stroke treatment. Indeed, the INSIST collaboration is currently searching for such opportunities.

Further collaboration during and beyond end of the project

In general, all companies indicate they would like to stay involved. As yet it does not always seem obvious to what extent they can be involved and what they can contribute, but they certainly consider the project of great value and would like to keep informed on the results. In return, the companies asked us for our view on further collaboration. We discussed several specific opportunities and the need to team up in new projects, involving R&D teams but also experts on regulatory issues.

Concluding remarks

While many critical questions were raised and while it was clear to all of us that this is a difficult road, there was broad consensus that in silico clinical trials have a good perspective for becoming a strong asset in better trial design in the field of acute ischemic stroke.

References

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