INSIST Clinical Focus Group Discussions at INSIST All hands workshop Milan – a Whitepaper

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Abstract:

In silico clinical trials hold the promise to use computational modelling of disease and its treatment to support the evaluation and introduction of new drugs and medical devices. The INSIST (In silico clinical trials for treatment of ischemic stroke) project aims to develop an in silico platform for the simulation and evaluation of novel treatments for acute ischemic stroke. INSIST comprises the generation of virtual patient populations, the in silico modeling of brain tissue death due to the lack of oxygen and nutrients following a stroke, thrombosis and thrombolysis, and thrombectomy. The combination allows in silico simulation of (pre-) clinical trials. The INSIST project organizes Focus Group Discussions involving specific stakeholders and contributors. In April 2019 Clinical Focus Group Discussions were organized to inform interested clinicians and to obtain their feedback on the concept, current state of the art, and intended further development of the INSIST project. In short, 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.

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 treated with "virtual" treatments. In silico clinical trials can potentially reduce, refine, and partially replace pre-clinical and phase 3 clinical trials. Moreover, in silico trials support the 3Rs: Replacement, Reduction, and Refinement of animal testing. 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 and 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 biomedical products for treatment of acute ischemic stroke. Such an in silico clinical ischemic stroke trial consists of the generation of populations of virtual stroke patients, in silico models of treatments, and in silico models 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 are presented and opportunities with stakeholders are discussed.

The INSIST Focus group concept goes beyond the communication of the results to our stakeholders at large. The Focus group concept is also a tool to develop the exploitation strategy. The Focus group discussions will 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 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 life time of the project.

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Methods

Focus group discussion

The first focus group discussion considered clinicians (intervention radiologists, neurosurgeons, and neurologists) and took place in conjunction with the all hands workshop in Milan in April 2019. 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.

After an introduction of in silico trials and INSIST in particular, a number of topics were offered to the participating medical specialists and they were asked to respond and give their expert opinion on these topics.

Points for discussion

The following topics were selected for discussion.

1. Clinical context and impact: to reduce, refine and partially replace human clinical trials;
2. Opportunities and limitations;
3. Selecting a topic for a relevant in silico trial for 4th and final year of the INSIST project as example for re-use of INSIST results e.g.:
   a. Simulate MRCLEAN NO-IV trial;
   b. Simulate new Prototype Thrombectomy Device trial;
   c. Simulate different populations (e.g. patients of age);
4. Exploitation and implementation;
5. White paper with focus on clinical relevance of performing in silico trial;
6. Further collaboration beyond end of project;

Setup of the discussion

Relevant stakeholders for this discussion were defined as clinicians (radiology, neurology) with extensive experience in treatment of acute ischemic stroke, notably by intra-arterial treatment, with further participation of a biomechanical engineer studying such treatment in large animals, a representative from pharma and the executive board of INSIST. Appendix 1 provides a listing of the members. The busy schedule of the stakeholders required separate discussions. 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. Each session started with a brief explanation of the INSIST goals and organization, followed by a discussion on a number of points as listed below

INSIST Clinical Focus Group Discussions

Current major issues limiting progress in treatment of acute ischemic stroke

It is recognized that in the treatment of patients with an acute ischemic stroke, there are still problems with (1) the thrombectomy technique and (2) the selection of patients.

Thrombectomy
By mixing aspiration and retrieval, successful treatment can be effective in up to 80%. From a clinical point of view, it is interesting to use modelling to understand why thrombectomy may not be successful (no recanalization) in 20% of the patients, and with that understanding set up an in silico stroke trial to virtually test a new design of a stentriever. It was noted that the MRCLEAN trial and MRCLEAN Registry, the recanalization rate as adjudicated by the

imaging core lab was a bit lower, between 60 and 70%. So indeed, there is room for further improvement of the technique, which is generally considered the most important issue in improving stroke treatment. Moreover, sometimes treatment takes longer than anticipated. It would also be good to have a smaller device with better navigation for the more distal occlusions, as it is hard to have a 3-4 mm device to be opened in a 1 mm vessel.

Patient selection
It is believed that collateral status forms a major determinant of functional outcome of patients with acute ischemic stroke. However, it is still not clear how to optimally evaluate collaterals and how to use this information for the selection of patients. As concerns evaluation of collaterals, a better understanding of brain tissue perfusions and the anatomy of the collateral circuits is required, as well an understanding how this is linked to radiological collateral scores. Concerning patient selection, recent trials suggest thrombectomy treatment up to as much as 24 hours after last seen well in patients with a good collateral status (Dawn, Diffuse trials). It would be very helpful to have a proper assessment of local tissue perfusion to better support patient selection.

In France, MRI is commonly used. The selection of patients based on MRI is not that well-developed as for CT. It may be hard to make MRI-based selection criteria to a more general patient selection, as more clinicians select patients based on CT scans.

It is recognized that around 5% of the patients have a different kind of pathogenesis for which thrombectomy will not work. It would be good to know beforehand when this is the case so that these patients can be treated differently.

Miscellaneous
Another interesting subject is to use modeling to understand why patients do not improve despite successful recanalization. There is a strong merit in studying the retrieved clots of the (60-80%) successful recanalization with varying reperfusion rates. Also, a better understanding of debris released during thrombectomy that may travel downstream and block the microcirculation, and the following chain of events, is required. This includes information on size distribution and composition. This knowledge needs to be included in the brain perfusion and infarction modelling.

Another subject that may be understudied within INSIST is the improvement of time to treatment. The effect of reperfusion/recanalization is expected to be much larger in the early treated patient groups than the late treated groups. Just improving the recanalization rate from 80 to 90% is not enough since treatment effect is also very much influenced by timing (how fast can patients be brought to the hospital and start the procedure).

Perception of the INSIST initiative

The clinical focus participants were impressed by the group of INSIST scientists with very different multidisciplinary backgrounds focusing on this single research subject, which is considered a major effort.

Moreover, the huge increase of interest in thrombectomy is welcomed. It is expected that the modelling of the thrombus, stent retriever and its interaction has predictive value.

Possible contribution of INSIST to solving current major issues

There are currently many options and combinations of current techniques to improve treatment. For instance, what would be the optimal combination of thrombolysis with rt-PA, stent-retriever thrombectomy, balloon guided catheters, use of an intermediate catheter, and direct aspiration with large bore catheter? These combinations of treatments can potentially be modelled within the INSIST context. Alternatively, new devices could be modeled. However, it is expected that for the next 5-6 years no new devices that

Figure 1 INSIST Clinical Focus group discussion. From left to right; Charles Majoie, Vanessa Blanc-Guillemaud, Luca Valvassori, and Matthew Gounis

significantly differ from the current ones will be introduced, because the investments on the current devices need to pay off. It is therefore recommended that INSIST would focus on the optimization of currently available techniques rather than to evaluate new methods. If, however, INSIST could demonstrate to clinicians that alternative, novel stentriever designs are better, clinicians could in turn pressure industry to improve their stentrievers. On the other hand, some companies have taken the direction of creating new retrievers, which perform a little better or adding aspiration or a device that forms a parachute.

The modelling of the extent of microthrombi that are produced by the different (combinations of) treatments should be of special interest.

It is believed that thrombolysis will keep an important place in stroke treatment. For many thrombectomy centers, transport of up to 60% of patients requires over two hours. It would be unethical not to treat patients when they cannot receive thrombectomy in time, but clearly, outcome falls dramatically with delay in this time window.

Another interesting issue, which appears to have been abandoned, is intra-arterial thrombolysis. It has been found that this treatment has limited value in large vessel occlusions, but some groups argue that there might still be an advantage, even when followed by mechanical thrombectomy. There is very little data about the effect of injecting the thrombolytic drug locally. A local injection of thrombolytic drugs could be very helpful for instance in patients with more distal occlusions or after mechanical thrombectomy of a proximal occlusion and a distal embolization. INSIST could help exploring the options for locally injected drugs in such patients.

On the other hand, it seems that the pharma industry is currently not investing in development of new thrombolytic drugs or administration routes beyond the common intra-venous administrated alteplase (rtPA) and the newer tenecteplase. Clearly, the success of thrombectomy has strongly limited the possibilities for sensible investments here. One participant remarked that "the inventor of a drug that could be given to stroke patient with guaranteed recanalization, should be given the Nobel prize". But there is not such treatment.

It was mentioned that tenecteplase could actually be better than rtPA. However, the treatment effect in stroke has to be determined based on the clinical score after 3 months. The difference between the two thrombolytic drugs is too small to demonstrate statistically significant improvements on this crude clinical scale for reasonable numbers of patients.

In silico trials could support decisions on go/no go of large-scale clinical trials of new drugs. Unlike actual trials, running large virtual populations would only require more computational time, and would allow exploring such options, leading to cost-effective trial design.

Within INSIST some efforts are underway to test alternatives (e.g. via ADAMTS13) and we may, given enough resources, virtually test such alternative treatments in an in silico stroke trial.

It is expected that there is a place for in silico trials in the near future. It will generate knowledge and reflection and might help to prove that a device works. In the end, the goal is to replace, refine and reduce animal experiments and eventually also clinical trials. In silico trials could de-risk drug development by industry.

In silico modeling can help gaining understanding of the microvasculature, among others by supporting experimental design and interpretation of experimental data. It is stressed that the aim of INSIST is not only to help in the development of new devices but also to understand the biology behind all these processes. Understanding the basic pathophysiology is a prerequisite to be able to create a validated in silico stroke trial. It is acknowledged that we are still lacking much basic understanding of the pathophysiology of brain tissue and blood vessels following a stroke event.

In silico trials use virtual populations and try to model the whole process at the population level. However, these computational models also hold opportunities towards personalized medicine, based on individualized diagnostic tests and treatment plans.

Do you foresee any risks for the INSIST approach?

The clinical experts were asked to identify the weak points of INSIST, by answering the question why the goal of INSIST could not be achieved.

The biology of the brain is considered to be extremely complex and dynamic. It was mentioned that the biology of the brain cannot be modelled with the limited information that we currently have. As a result, there are some doubts about how a new solution or medication can be found for a biological problem that we do not yet understand.

In the same line, a weak point of the project was considered to be the modelling of clinical/functional outcome. The INSIST approach is to computationally model the location and volume of the final infarct and use that as input to a statistical model to then predict clinical outcome. This statistical model will be trained on available trial data of some 3000 patients. Successful prediction of infarct size and location does not mean that estimation of the clinical outcome of patients after successful or unsuccessful treatment is accurate. Clinical outcome depends on many variables. As an example, clinical outcome strongly depends on neurological care of patients after stroke. It therefore is important to also simulate clinical outcome. Within a large population, a statistical approach may accurately describe the treatment effect, since patient-specific issues that are not covered by the models, including care, may average out.

Moreover, it was stated that the role of collaterals may be too difficult to model with the limited knowledge that we currently have. However, there seems to be agreement that the anatomy of the pial surface may also be important to understand the characteristics of collateral flow.

The validation based on animal models is tricky. "You cannot compare arteries of rabbits that eat carrots every day with arteries of French patients that eat cheese every day". So, it will take some time before the in silico trials will actually replace the real world. Nevertheless, validation, even in animal models, is a big step forward.

It was mentioned that stroke is a dynamic process, the thrombus always moves more distal. It may be difficult to model the whole dynamic interacted processes rather than a number of single events.

In silico trials planned in the fourth year

With the importance of patient selection, INSIST could focus on selection, running different trials with different selections of patients and assess the outcome of such trials assessing (novel combinations of) existing or new treatment modalities.

Further exploitation of INSIST results

After success of an in silico clinical trial, these efforts should be reused to improve personalized health care predicting optimized treatment for individual patients, though this is not the focus of the current project.

Concluding remarks

In general, INSIST is considered a promising initiative to perform in silico clinical trials, it will generate knowledge and reflections and might help prove that devices work. In the end, the goal is to refine, reduce and partially replace animal and human experiments and support clinical trials. There may be a larger role for thrombolysis in the near future, despite that this has received much less attention in the literature lately.

Appendix 1: participants of the INSIST Clinical Focus Group Discussions

The participants of the INSIST clinical focus group discussions consisted of

Luca Valvassori, Interventional neuroradiologist, San Gerado Hospital, Monza, Italy;

Ana Paula Narata, Interventional neurosurgeon, University of Geneva, Genève, France;

Matthew Gounis, professor radiology and biomedical engineer, University of Massachusetts, USA;

Vanessa Blanc-Guillemaud, Clinical and translational research leader, Servier, France;

Aad van der Lugt, Neuroradiologist, Erasmus MC, Rotterdam, the Netherlands

Diederik Dippel, Neurologist, Erasmus MC, Rotterdam, the Netherlands;

Yvo Roos, Neurologist, Amsterdam UMC, Amsterdam, the Netherlands;

Hester Lingsma, Epidemiologist, Erasmus MC, Rotterdam, the Netherlands;

Charles Majoie, Interventional neuroradiologist; Amsterdam UMC, Amsterdam, the Netherlands;

Alfons Hoekstra, Computational scientist, University of Amsterdam, Amsterdam, the Netherlands;

Ed van Bavel, Biomedical Engineer, Amsterdam UMC, Amsterdam, the Netherlands;

Henk Marquering, Biomedical Engineer, Amsterdam UMC, Amsterdam, the Netherlands;

Laurian Langejan, Project Manager, Amsterdam UMC, Amsterdam, the Netherlands;