InSilicoNEURO

MS TreatSim

Virtual Patients for informed clinical trial design in Multiple Sclerosis

Multiple Sclerosis is caused by an autoimmune reaction against the central nervous system's protective myelin sheaths.

This loss of myelin sheaths causes neurological symptoms, which vary between patients, but often present in a characteristic relapsing-remitting pattern (Relapsing-Remitting Multiple Sclerosis, RRMS), while patients slowly accumulate disability. In the past few decades, more than 10 disease modifying therapies for RRMS have been successfully brought to the market. These drugs have completely transformed the RRMS therapeutic landscape, providing RRMS patients with a much brighter outlook.

However, these developments have consequences for clinical trial design in MS. For example, in new clinical trials, the placebo arm may need to be replaced by an active comparator arm. Also, currently available clinical trial populations typically display earlier and milder disease courses than those in "historical" trials (1). This has led to new challenges for pharma companies developing MS therapies:

- More expensive trials, as a result of the need for larger group sizes and longer trial durations due to lower relapse rates (annual relapse rates of 0.16-0.37, vs 0.5-0.87 before 2002 (2))
- Higher failure risks due to smaller differences between arms (1) and differential responses of MS patients to treatment (3)
- Difficult comparison of new drugs with drugs already on the market due to large differences in trial methodology and population characteristics (2)

What is MS TreatSim?

The Multiple Sclerosis Treatment Simulator is the result of a collaboration between University of Catania's spin-off Mimesis and InSilicoTrials Technology.

MS TreatSim is a web-based application that enables simulation of realistic disease courses in RRMS, based on a mechanistic model of the immune system and its dysregulation in MS (4).

The model incorporates the adaptive and innate immune system, the autoimmune response and four distinct disease modifying therapies. Due to implementation of immune system heterogeneity and variable disease severity based on basal patients' characteristics, the virtual patients' disease courses and response to treatment display real-world variability. The relapse rates predicted by the model have been validated with individual clinical data (4), as well as clinical trial data.

MS TreatSim combines two different types of simulation workflows. In the first simulation workflow, In Silico Trial, MS TreatSim enables simulation of clinical trials with heterogeneous populations of virtual RRMS patients. This workflow can be used to explore trial design scenarios in terms of duration, population, active comparator or placebo and choice of outcome measures.

The second simulation workflow, Digital Twin, is designed for exploring the effect of treatment strategies at the individual level.

Advantages

Perform simulations with a validated state-of-the-art mechanistic model of RRMS and four commonly prescribed treatment options: IFNβ-1a, teriflunomide, natalizumab, and ocrelizumab.

Customize a virtual population's base characteristics and disease activity to predict size of treatment effects

Assess not only relapse rates, but also immune system based secondary outcome measures

Investigate heterogeneity of treatment result at both population and individual levels

Optimize phase II clinical trial designs

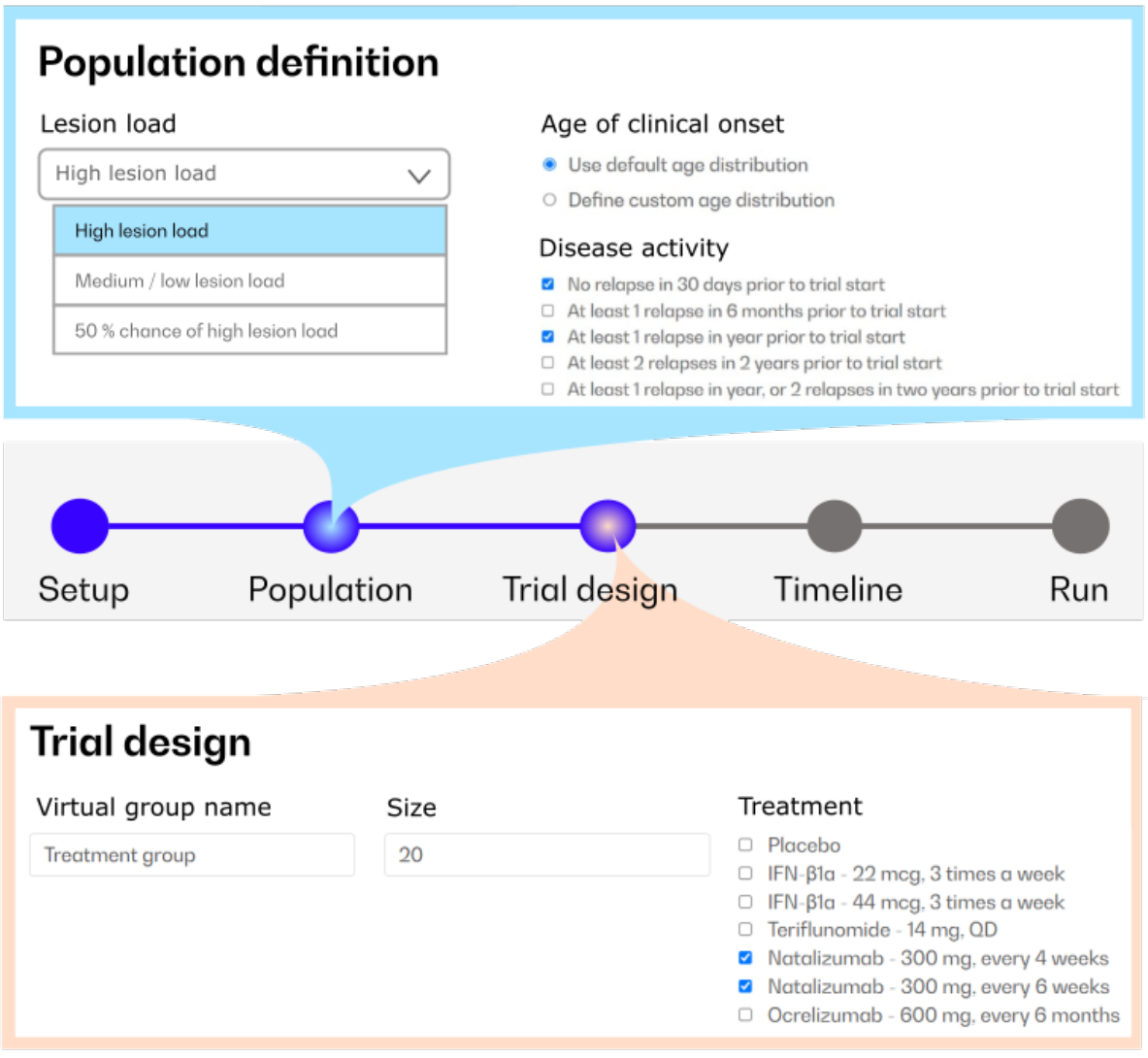
Download data for further analysis

How it works

The In Silico Trial Workflow: Explore population level effects.

MS TreatSim's In Silico Trial workflow enables setup and simulation of a population level simulation in a user-friendly way by using a step-by-step integrated workflow

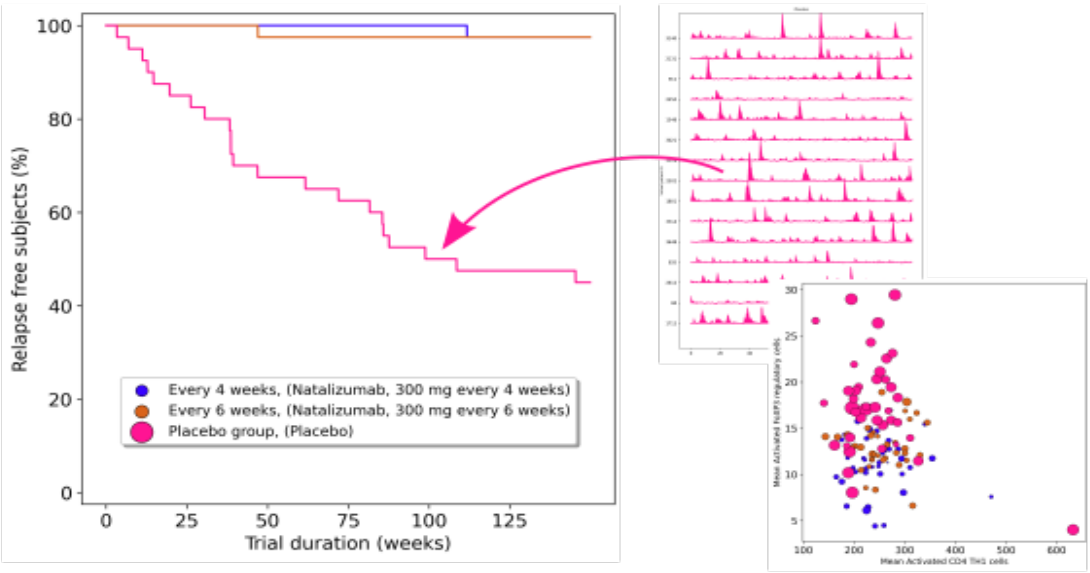
- Define the population by setting basal characteristics and activity criteria
- Insert unique groups that will receive placebo or one of selected treatment options
- Choose trial length and intermediate analysis time points



After running the simulation, results will be available as:

- Population-level relapse statistics
- Individual relapse rates and lesion activity
- Individual immune system variables

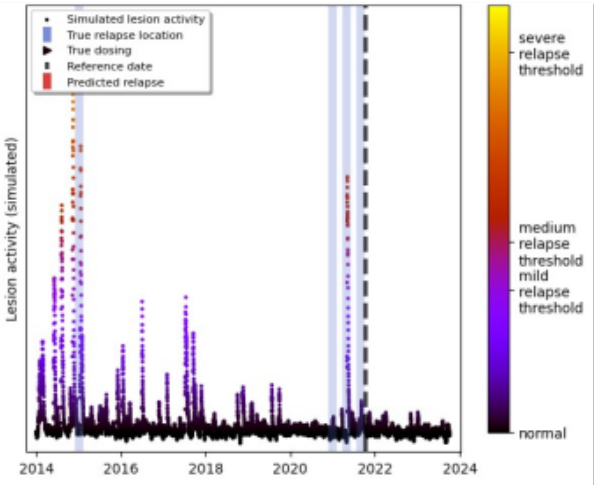
		Every 4 weeks	Every 6 weeks	Placebo group
		Natalizumab - 300 mg, every 4 weeks	Natalizumab - 300 mg, every 6 weeks	Placebo
Number of relapses		1	2	40
Relapse-free subjects	%	97.5	97.5	45.0
Annualized relapse rate	1/year	0.009 ± 0.054	0.017 ± 0.109	0.348 ± 0.389
Time to relapse	years	2.9 ± 0.1	2.8 ± 0.3	1.8 ± 1.1



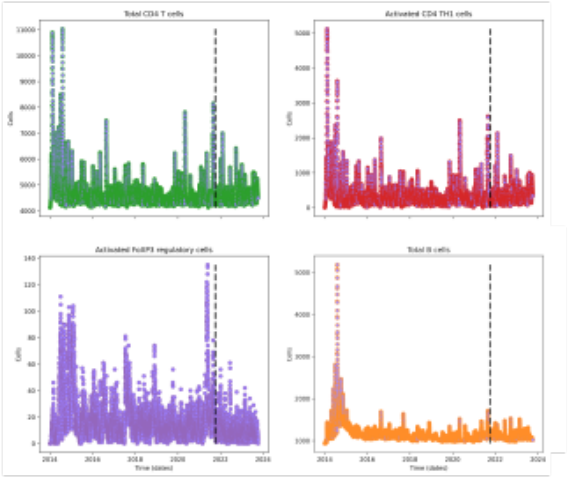
The Digital Twin Workflow: Obtain insight into treatment effects at the individual level.

- Create a patient profile based on disease history and characteristics
- Run model calibration to generate a digital twin
- Select treatment options to explore
- Compare effect of treatment on relapse rate and immune dynamics

Predict relapse rates



and underlying dynamics



Integrate a custom treatment

The full mechanistic model provides a unique opportunity to integrate a novel drug targeting the immune system. Contact us to explore possibilities.

In silico is key to innovate drug development

Today, the very long and expensive development and the complex registration processes for new drugs are becoming financially unsustainable.
Regulatory agencies have been encouraging the use of in silico methods in drug research and development for years (5) because the use of these methods can greatly accelerate the time-to-market of new medicines for the benefit of the patients while significantly reducing development costs and allowing companies to exploit patents for a longer period. Solvers, IT infrastructure and computational specialists require a continuous investment from companies.

To help solve these challenges, **InSilicoTrials Technologies** has developed a game-changing-solution. Our experts:

Select computational models from outstanding research centers around the world

Integrate them in our cloud-based platform

Make them available through user-friendly online products

This solution enables companies to leverage cutting-edge in silico methods at low costs without specific computational expertise, IT infrastructure and solvers investments requirements. On our cloud-based platform, users can select the online computational product of their choice in pay-per-use, or ask us to build the digital product they need.

Why working with InSilicoTrials

SaaS

Buy tokens and use the online products of your choice among those available on the platform

VIRTUAL PATIENTS

Design and accelerate your clinical trials with the virtual patient populations you need

ON DEMAND & CUSTOM

Ask us for the models and simulations you need, or ask us to evaluate where modeling and simulation can support you

TECHNOLOGY-ENABLED SERVICES

Ask us for support on technology integration, in silico trials planning, execution and reporting, in line with regulatory requirements

References:

1. Zhang Y, Salter A, Wallström E, Cutter G, Stüve O. Evolution of clinical trials in multiple sclerosis [Internet]. Vol. 12, Therapeutic Advances in Neurological Disorders. SAGE Publications Ltd; 2019 [cited 2021 Mar 31]
2. Montalban X. Review of methodological issues of clinical trials in multiple sclerosis. J Neurol Sci [Internet]. 2011 Dec [cited 2021 Oct 12];311(SUPPL. 1).
3. Manouchehri N, Zhang Y, Salter A, Hussain RZ, Hartung H-P, Hemmer B, et al. Clinical trials in multiple sclerosis: potential future trial designs. 2019 May 13 [cited 2021 Oct 12];12.
4. Pappalardo F, Russo G, Pennisi M, Parasiliti Palumbo GA, Sgroi G, Motta S, et al. The Potential of Computational Modeling to Predict Disease Course and Treatment Response in Patients with Relapsing Multiple Sclerosis. Cells [Internet]. 2020 Mar 1 [cited 2021 Feb 25];9(3):586.
5. U.S. Food and Drug Administration. Challenge and Opportunity on the Critical Path to New Medical Products [Internet]. Review Literature And Arts Of The Americas. 2004 [cited 2021 Oct 12].

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