MS TreatSim: A clinical trial simulator for Relapsing-remitting Multiple Sclerosis

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INTRODUCTION

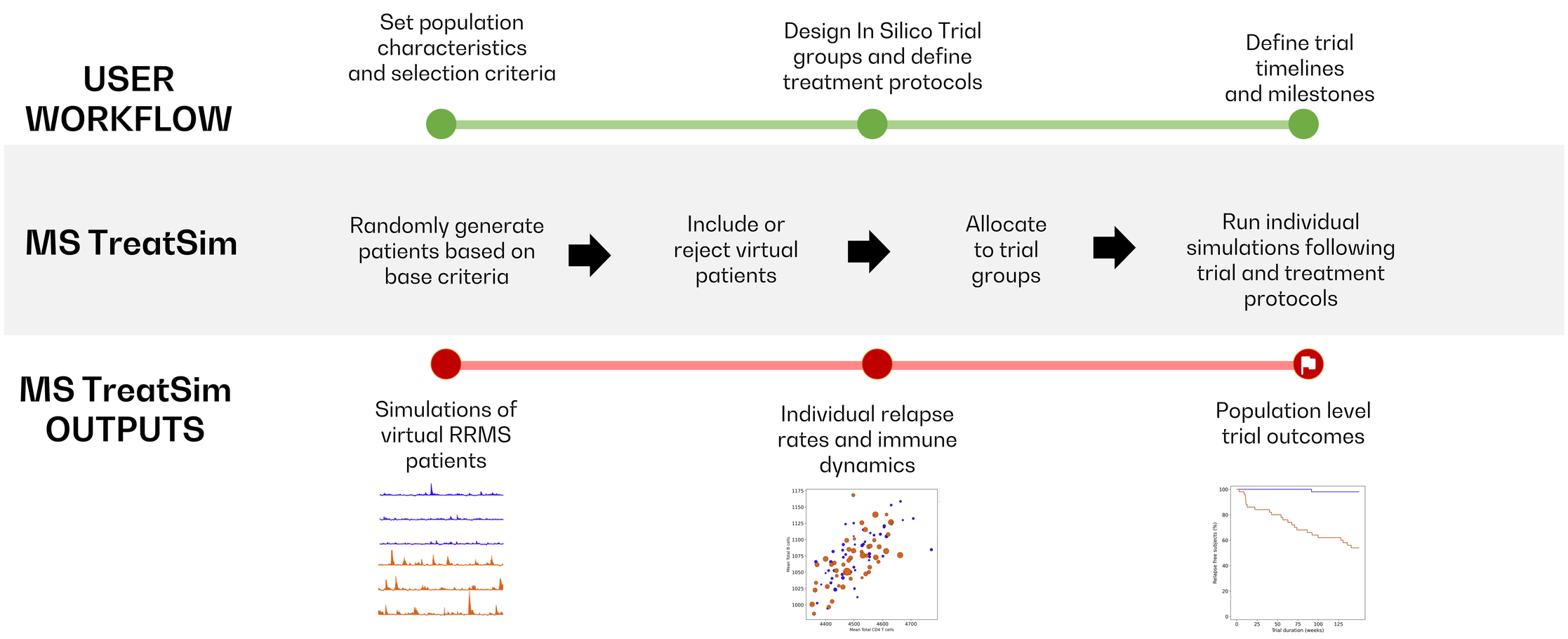
Relapsing-remitting Multiple Sclerosis (RRMS) diagnostic methodologies and treatment options have seen great advances in the last decades [1]. Although positively affecting patient care, these developments have also impacted clinical trial design. For example, with the increased availability of treatment options, placebo-controlled trials have been progressively replaced by active comparator trials. Moreover, the average annualized relapse rate has declined over the last decades [2], thus requiring larger groups sizes and/or longer trial durations.

OBJECTIVES

- **To develop a trial simulation framework for *in silico* trials in Relapsing-remitting Multiple Sclerosis**
- **To reproduce the control group characteristics and treatment effect of a historical clinical trial of natalizumab with the simulator**

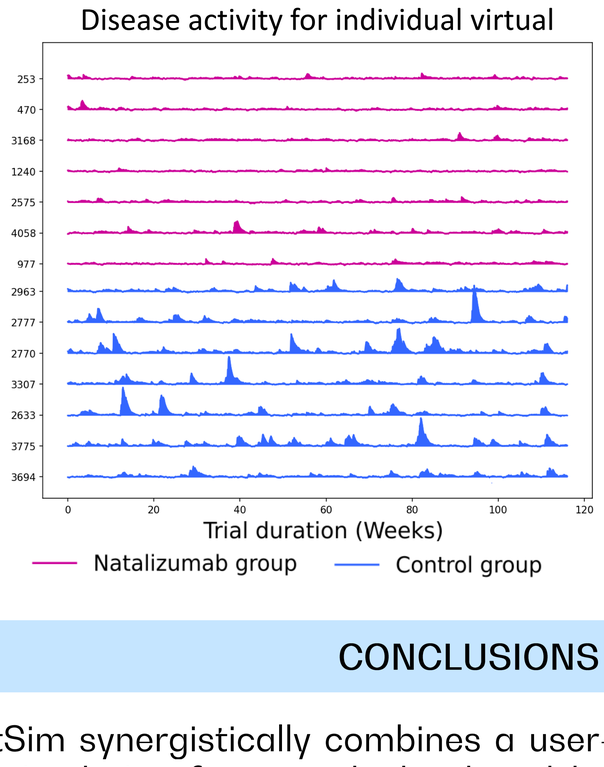
METHODS

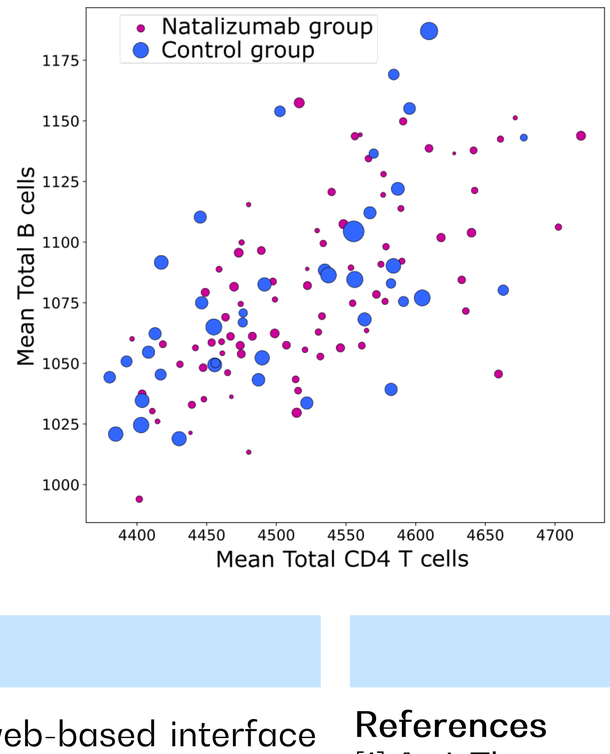
The trial simulator (MS TreatSim, [3]) consists of a web-based, user-friendly simulation framework to set up and run *in silico* trials. The underlying mechanistic model is based on an agent-based framework, incorporating detailed representations of the innate and adaptive immune system components, including B cells, T helper cells, T regulatory cells, cytotoxic T cells, natural killer cells, antigens, and cytokine signaling [4]. For application to RRMS, the model was expanded with the autoimmune response and the brain's oligodendrocytes. Treatments, such as natalizumab, are modelled via their mechanism of action at the cellular level [4]. We applied MS TreatSim to reproduce *in silico* the AFFIRM clinical trial for natalizumab [5]. Mirroring the clinical study [5], two groups of virtual patients were created with a treatment control ratio of 2:1; the age of onset distribution was set to 49.4% 158 : 36.2% : 14.4% (18-29, 30-39 and 40-49 years), lesion load was set to high and oligoclonal bands status to present for all virtual patients, simulation duration prior to the trial was set at 5 years, and virtual patients were only included if they had experienced at least one relapse in the year preceding inclusion, but not in the final month. The natalizumab group (n=80) was treated *in silico* with 300 mg of natalizumab every 4 weeks for 104 weeks, while the control group (n=40) remained treatment naïve.

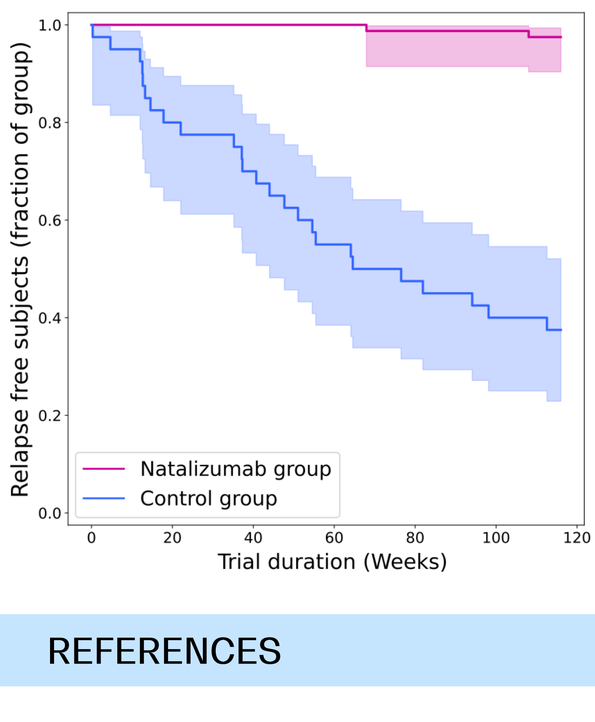


RESULTS

Simulated two years relapse free survival indicated good agreement between observations and model predictions (control group: 41% in [5] vs 40% in silico). In the treatment group, the treatment effect was clear in both clinical and in silico studies (67 % vs. > 90%). An explanation for this overestimation may lie in the fact that resistance mechanisms are currently underrepresented by the *in silico* trial setup of this study.







CONCLUSIONS

MS TreatSim synergistically combines a user-friendly web-based interface with the simulation framework developed here, as well as an underlying mechanistic model. MS TreatSim can be used to explore effectively clinical scenarios, accelerating optimization of clinical trial designs.

REFERENCES

References

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