Journal of Biomechanics 176 (2024) 112335

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech

In Silico clinical trial to predict the efficacy of hip protectors for preventing hip fractures

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ARTICLE INFO

Keywords:
Osteoporosis
Hip fracture
Hip protector
In Silico medicine
In Silico trial

ABSTRACT

Osteoporosis is characterized by loss of bone mineral density and increased fracture risk. Reduction of hip fracture incidence is of major clinical importance. Hip protectors aim to attenuate the impact force transmitted to the femur upon falling, however different conclusions on their efficacy have been reported; some authors suggest this may be due to differences in compliance. The aim of this study was to apply an *In Silico* trial methodology to predict the effectiveness of hip protectors and its dependence on compliance.

A cohort of 1044 virtual patients (Finite Element models of proximal femur) were generated. A Markov chain process was implemented to predict fracture incidence with and without hip protectors, by simulating different levels of compliance. At each simulated follow-up year, a Poisson distribution was randomly sampled to determine the number of falls sustained by each patient. Impact direction and force were stochastically sampled from a range of possible scenarios. The effect of wearing a hip protector was simulated by applying attenuation coefficients to the impact force (12.9 %, 19 % and 33.8 %, as reported for available devices). A patient was considered fractured when impact force exceeded the femur strength.

Without hip protector, virtual patients experienced 66 ± 5 fractures in 10 years. Wearing the three devices, fracture incidence was reduced to 43 ± 4, 35 ± 4 and 17 ± 2 respectively, at full compliance. As expected, effectiveness was dependent on compliance.

This *In Silico* trial technology can be applied in the future to test multiple interventions, optimise intervention strategies, improve clinical trial design and drug development.

1. Introduction

Osteoporosis is characterised by low bone mineral density (BMD) and bone architecture deterioration, which is associated with increased probability of sustaining fragility fractures and increased mortality (Kanis et al., 2019). Fragility fractures can occur at e.g. the wrist, ankle, spine and hip, and among those hip fractures are of particular concern given their severe socioeconomic impact. It has been reported that 17–32 % of deaths after 1 year of a hip fracture are directly related to the fracture itself (Kanis et al., 2003; Tarazona-Santabalbina et al., 2012). Nevertheless, the incidence of fractures in the population is relatively low, with 7–10 hip fractures per 1000 person years (Brauer et al., 2009; Schuit et al., 2004). Therefore, one of the major challenges when testing and/or developing interventions and treatments is the need to recruit large cohorts to measure significant effects on fracture outcomes.

More than 90 % of hip fractures are positively associated with a fall event (Komisar and Robinovitch, 2021). Strategies to reduce hip fractures include the use of protective devices (to reduce the impact force transmitted to the femur upon falling), exercise and balance training (to improve balance and reduce fall rate), pharmacological treatments (to increase bone mineral density and therefore improve the mechanical strength of the femur) (Cumming and Klineberg, 1994; Hayes et al., 1993). In this study, we focused on hip protectors, which, if worn correctly, may have an immediate effectiveness (Bentzen, Bergland and Forsén, 2008; Korall et al., 2019). Nevertheless, no conclusive evidence of their effectiveness is available, especially in community-dwelling individuals (Santesso et al., 2014). Likely, poor compliance (low usage rate) remains a major factor that limits effectiveness (Santesso et al., 2014). It has been reported that compliance can be as low as 20 % (O'Halloran et al., 2004), especially in community-dwelling settings. Additionally, compliance is challenging to accurately track, which impairs the assessment of device's effectiveness.

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https://doi.org/10.1016/j.jbiomech.2024.112335
Accepted 17 September 2024
Available online 18 September 2024

Computer modelling and simulation could constitute an important tool for testing and/or developing interventions for the reduction of fracture incidence, with improved time- and cost-effectiveness. For this application, i.e. where models are used for the development and assessment of biomedical products, the term "*In Silico* clinical trial" was introduced in 2011 by the VPH (Virtual Physiological Human) institute (Viceconti, Henney and Morley-Fletcher, 2016). *In Silico* trials can also be applied to supplement clinical trials with virtual patients thus increasing sample size, or to explore less common phenotypes, or to improve clinical trial design (Viceconti, Henney and Morley-Fletcher, 2016).

Computational models for the assessment of fracture risk in the proximal femur have been extensively investigated. Finite element (FE) models based on Computed Tomography (CT) data have been validated for the prediction of femur strength, which is one of the major determinants of fracture risk (Bessho et al., 2009; Keyak et al., 2005; Koivumäki et al., 2012; Nishiyama et al., 2014; Viceconti et al., 2018). In validation studies on cadaver bones, FE models were able to predict failure load with standard error of estimate (SEE) of 15 %, and strains with SEE of 7 % (Schileo et al., 2014; Viceconti et al., 2018). FE predictions have also shown superior stratification accuracy in retrospective cohorts, compared to aBMD. In (Enns-Bray et al., 2019), FE models were used to compute ΔMVS (change in maximum volumetric strain), which could stratify fractured and non-fractured patients with higher accuracy (area under the receiver-operator curve AUC = 0.85, when fall history was known) compared to aBMD (AUC = 0.74). In Bhattacharya et al. (2019), FE models were integrated in a multiscale approach to predict current absolute risk of hip fracture (ARF0). This multiscale model takes into account, in addition to femur strength, fall rate, stochasticity of fall scenarios, and impact attenuation factors due to postural reflex and passive attenuation components. ARF0 could classify fractures in a retrospective cohort of postmenopausal women with AUC = 0.852, 77.6 % specificity and 81.6 % sensitivity (Bhattacharya et al., 2019).

In this study, this approach has been adapted for the development of an *In Silico* trial technology (hereafter called *BoneStrength*) to predict fracture incidence in a cohort of virtual patients. In a previous work from our group, a methodology has been developed to generate virtual patients using a statistical atlas based on CT scans of 94 post-menopausal women (La Mattina et al., 2023). Subsequently, a placebo and an intervention group can be simulated, and the reduction in fracture incidence could provide a prediction of the intervention effectiveness. To predict fracture incidence, we used a Markov chain process in combination with our mechanistic model. Markov chain approaches have been used in previous cost-effectiveness analyses on interventions for preventing falls and/or fractures (Church, Haas and Goodall, 2015; Svedbom et al., 2019), although transitions between states were only based on odds ratios data from literature or other sources.

The aim of this study was to develop an *In Silico* trial methodology (*BoneStrength*) for osteoporosis interventions and to present a first application to predict the effectiveness of hip protectors in reducing hip fracture incidence in a cohort of postmenopausal women, as well as the effect of compliance. This constitutes a first step towards the development and validation of an *In Silico* trial for the assessment and development of osteoporosis interventions and treatments.

2. Materials and methods

2.1. Virtual population

A cohort of 1044 virtual patients (T-score –1.02 ± 1.01, ARF0 42.9 ± 21.9 %) was generated from a cohort of 94 postmenopausal women for which CT scans of the proximal femur were available (La Mattina et al., 2023). In the physical cohort, 47 subjects had previously experienced a hip fracture, while 47 were height- and weight-matched women (with no previous hip fractures) (Yang et al., 2014). The physical cohort was used to generate a statistical anatomy atlas including geometrical and density features, through principal component analysis. The atlas was subsequently up-sampled to generate virtual patients. The cohort size was selected to approximately reproduce a Phase III clinical trial, which typically requires at least 1000 patients.

2.2. Fall model

The multiscale model applied to simulate side falls and predict the associated impact forces has been previously described (Bhattacharya et al., 2019) and is briefly summarised here. In the multiscale model three different components are identified at three space–time scales and orchestrated:

1. Body-floor impact model to calculate impact force upon falling (whole-body scale).
2. Ground-skeleton force-transfer model to calculate the portion of the impact force transmitted to the proximal femur, taking into account the attenuation due to different factors (intermediate scale between whole-body and organ scale).
3. Finite element (FE) model to calculate femur strength (Paragraph 2.3) (organ scale).

In the first model, the patient's body is modelled as an inverted pendulum with a hinge constraint corresponding to the feet. Intensity of the force at impact with the ground is calculated based on patient-specific height and weight. Five stochastic parameters are included to account for the variability in fall conditions: initial angular velocity and acceleration, angles between the vertical axis and the body at the initial and final time points, and attenuation due to postural defence (Bhattacharya et al., 2019). In the second model, the force transmitted to the femur is obtained by taking into account the attenuation due to several factors: passive soft tissues thickness, flooring material, presence of external devices such as hip protectors, contraction of active soft tissues. Soft tissue thickness (STT) is estimated based on body mass index (BMI) as reported in previous studies (Dufour et al., 2012; Schacter and Leslie, 2014), which is assumed constant for each virtual patient:

$$STT[cm] = 0.23415 * BMI\left[Kg\, m^{-2}\right] - 3.3444$$

Therefore, attenuation coefficient (η_{ST}) is estimated as follows (Bhattacharya et al., 2019):

$$\eta_{ST} = 0.0231 * BMI - 0.33$$

The other factors (flooring material, external devices, contraction of active soft tissues) are modelled empirically by introducing a stochastic attenuation parameter. Each of the six stochastic parameters can vary within a specific range obtained from the literature and described by a normal distribution within the defined range, symmetrically truncated at ±3 standard deviations (Bhattacharya et al., 2019).

In this work, the effect of muscle contraction was considered negligible, under the assumption that in elderly patients the delay in reaction times exceeds fall time (St George et al., 2007). Three hip protectors were simulated, using the attenuation coefficients reported in a previous study (Laing and Robinovitch, 2008). Considering an impact velocity of 1–3 m/s, the maximum reported attenuation was 33.8 % (66.2 % of the impact force transmitted to the femur), while the minimum was 12.9 %. On average, impact attenuation was 19 % considering all tested devices. Compliance was simulated as an unbiased probability that the patient wore the hip protector upon falling.

2.3. Finite element (FE) models

In FE models (ANSYS Mechanical APDL 2020R1, ANSYS Inc., USA), the proximal femur geometry was meshed with 10-node tetrahedral

elements and heterogeneous material properties. In the original cohort, patient-specific and element-specific Young's Moduli were assigned based on local CT density (Altai et al., 2019; Qasim et al., 2016), which were subsequently used to generate the anatomical atlas and assign local density in virtual patients through principal component analysis (La Mattina et al., 2023). Boundary conditions to simulate a fall on the side were defined with the femur rotating around the knee centre and a non-linear contact between the greater trochanter and a rigid plane. Impact force was applied at the centre of the femoral head (Altai et al., 2019; Qasim et al., 2016). Directions of the impact force varied within a range of possible scenarios, and were sampled stochastically for each fall (Paragraph 2.4). A sample load of 1000 N was applied with a linear simulation and failure load was obtained by rescaling the sample load, adopting a maximum principal strain failure criterion, as the force for which the peak strain over a sphere of 3 mm reached a value of 0.73 % first principal strain or 1.04 % third principal strain (Bayraktar et al., 2004; Schileo et al., 2008).

FE models were solved using High-Performance Computing (in approximately 20 min with 4 cores and 28 GB of RAM per simulation; Galileo100, CINECA, Italy).

2.4. Markov chain process

A Markov chain process was implemented for the simulation of the *In Silico* trial (Fig. 1), enabling to predict fracture incidence, which is the primary endpoint in Phase III clinical trials. The pipeline was implemented and automatized using Batch, and standard Python libraries NumPy and SciPy.

The occurrence of falls was modelled as a Poisson distribution. At each simulated follow-up year, a Poisson distribution with λ (expected rate of occurrences) equal to 0.65 falls/year (Gillespie et al., 2012) was randomly sampled to determine the number of falls for each patient. Impact force and direction for each fall event were stochastically sampled from a range of possible scenarios. Direction angles could vary from –30° to +30° in the antero-posterior direction and from 0° to 30° in the medio-lateral direction (Fig. 1). Impact force was obtained by sampling each stochastic parameter from the associated distribution (Bhattacharya et al., 2019). A patient was considered fractured if the impact force exceeded the femur strength in the corresponding direction. When a patient fractured, it was excluded from the cohort and subsequent falls were not simulated. Convergence of the stochastic process, in terms of predicted number of fractures, was reached with 20 realisations. Each realisation included approximately 7000 falls for a total of approximately 500 k core-hours to simulate ~1000 patients and 10 years follow-up.

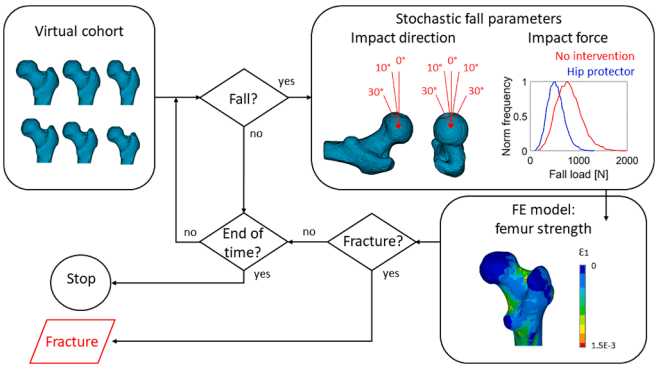

Fig. 1. Overview of the methods. For each virtual patient, side falls are simulated over a follow up period of 10 years. For each simulated fall event, fall parameters are sampled stochastically from a range of possible scenarios. Finite Element (FE) models are used to predict the femur strength. A patient is considered fractured when impact force exceeds femur strength in the corresponding loading direction.

Predicted incidence of hip fractures and effectiveness of hip protectors were compared with the ranges reported in clinical literature.

2.5. Statistical analysis

The effectiveness of hip protectors was evaluated by obtaining Risk Ratio (RR) between fracture incidence in the intervention and control groups. RR was calculated as the number of hip fractures at convergence predicted in the hip protector group divided by the number of fractures in the control group, given that sample size was equal in both arms.

3. Results

Cumulative number of fractures over a 10-year follow-up period (N = 1044) is reported in Fig. 2a, while total number of fractures for different levels of compliance is reported in Fig. 2b for the three simulated hip protectors (attenuation coefficients of 12.9 %, 19 % and 33.8 %). Without hip protector, predicted fall impact forces were in the range of approximately 200–2300 N (Fig. 1), and virtual patients experienced 66 ± 5 fractures in 10 years. Wearing the hip protector, impact forces were in the range of approximately 150–1500 N (Fig. 1). Fracture incidence was reduced to 43 ± 4, 35 ± 4 and 17 ± 2 fractures respectively, at full compliance. Risk ratio (RR) was 0.65, 0.53 and 0.26 for the three devices. As expected, effectiveness was dependent on compliance. For an average compliance of 60 % as reported in a recent study (Korall et al., 2019), RR was 0.80, 0.74 and 0.65, respectively.

4. Discussion

The aim of this study was to develop an *In Silico* trial (*BoneStrength*) for osteoporosis interventions and apply the methodology to predict the efficacy of hip protectors. The method was used to successfully simulate the equivalent of a Phase III clinical trial with more than 1000 virtual patients for each cohort, and predict fracture incidence, which is the primary endpoint requested by regulators. *BoneStrength* represents the first *In Silico* trial in the field of osteoporosis treatments. The methodology applied to simulate side falls was based on a Digital Twin for the prediction of patient-specific fracture risk (Bhattacharya et al., 2019). In this study, the model was adapted and integrated into a Markov chain process to enable the prediction of fracture incidence at the population level, a crucial step for the simulation of a full-blown clinical trial *In Silico*. Additionally, this approach significantly improved computational efficiency; fracture risk was obtained by solving 28 FE models per patient (28 impact directions), which would require approximately 1 million core-hours to simulate ~ 1000 virtual patients and 10 years follow-up. In *BoneStrength*, each realisation of the Markov chain process included approximately 7000 falls for a total of approximately 500 k core-hours. The availability of this automatized pipeline enables the simulation of a large number of scenarios of interest. A first application to assess the effectiveness of hip protectors, although relatively simple, was used to demonstrate the applicability of the methodology.

Results show that hip protectors are effective in reducing fracture incidence, when regularly worn. As compliance decreases, the probability of unprotected falls increases, and efficacy decreases almost linearly with compliance. The majority of previous clinical studies reported no conclusive or little evidence that hip protectors are effective, especially in community-dwelling settings. A systematic review (Santesso et al., 2014) reported a small reduction in hip fractures in residential care settings (RR = 0.82), while no evidence of effectiveness in community-dwelling subjects (RR = 1.15). Compliance was likely the major problem associated with low effectiveness and subsequent lack of evidence. Among studies reporting no benefit, compliance was poor. Adherence was 35.9 % by the end of the study (10 months) in (Hubacher and Wettstein, 2001). Birks et al. (2004) reported a compliance of 31 % participants who were still wearing the device "most of the time" at 12 months. O'Halloran et al. (2004) reported a compliance of 23.2 % at 48

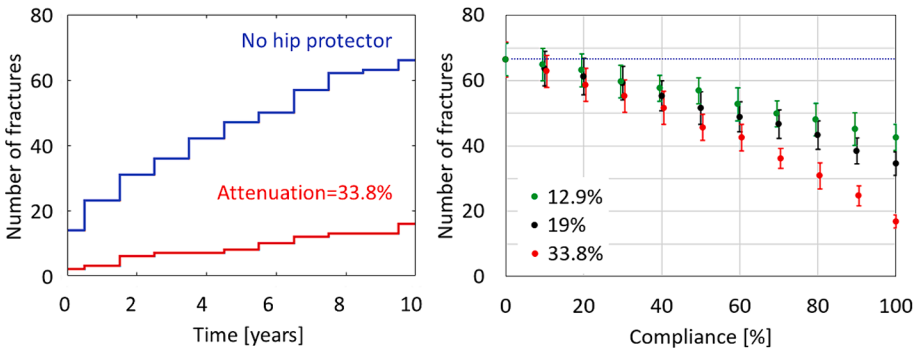

Fig. 2. Predicted cumulative number of fractures (a) and total number of fractures depending on compliance (b) in 10 years (N = 1044 virtual patients) for three hip protectors characterised by different attenuation coefficients (12.9 %, 19 % and 33.8 %).

weeks and 19.9 % at 72 weeks. Cameron et al. (2011) reported adherence of 24–25 % at 6 months, and only 22.2 % and 6.5 % of protected falls in the two intervention groups (with various hip protectors). In more recent studies, higher effectiveness (Korall et al., 2019) and cost-effectiveness (de Bot et al., 2020) have been reported. In (Korall et al., 2019), a significant reduction in hip fractures (RR = 0.36) was observed by using hip protectors. The effect of compliance was compensated by comparing protected vs. unprotected falls, as opposed to comparing users vs. non-users. Additionally, as the study was conducted in long-term care residencies, compliance was higher (60 % of total recorded falls were protected). Fracture incidence reported in this study was 0.6 % in terms of falls resulting in a hip fracture (20 fractures per 3520 falls) (Korall et al., 2019). Devices used in this study were a variety of Hipsaver and Safehip protectors, for which attenuations are in the range of 17.5–34 % (Laing et al., 2011). These experimental results are in good agreement with predictions of our *In Silico* study. *BoneStrength* predicted a fracture incidence of 0.57 %-0.65 % for the corresponding hip protectors (43 ± 4 fractures over 7552 ± 126 falls with 33.8 % attenuation; 49 ± 5 fractures over 7552 ± 126 falls with 19 %), considering the same compliance level (60 %). Predicted RR was in the range of 0.26–0.53, while the clinical study reported RR = 0.36 (Korall et al., 2019).

A limitation of this study is that the virtual population was generated based on the Sheffield cohort (Yang et al., 2014), which included a relatively low number of subjects (94 community-dwelling post-menopausal women, 50 % of which experienced a previous hip fracture) with homogeneous ethnicity. Nevertheless, this cohort was considered representative of a population that would be prescribed hip protectors, i.e. fragile individuals at higher risk. In previous studies, participants have been usually recruited in presence of one or more risk factors (Birks et al., 2004; Cameron et al., 2011; Hubacher and Wettstein, 2001), and up to 68 % of participants had experienced a previous fragility fracture at various skeletal sites.

The model used to predict impact force transmitted to the femur during a side fall was simplified. In previous studies (Fleps et al., 2019; Majumder, Roychowdhury and Pal, 2013), the effect of hip compliance due to soft tissues and anthropometric variations on the impact force have been explicitly modelled, while in this study some aspects were moved to stochastic uncertainty. Nevertheless, previous studies (Fleps et al., 2019; Majumder, Roychowdhury and Pal, 2013; Robinovitch, McMahon and Hayes, 1995) reported that the relationship between STT and impact force attenuation is approximately linear. For this reason, we have implemented the influence of STT as an attenuation coefficient, without modelling soft tissues explicitly in the FE models. The variability in height, weight and STT was taken into account by generating a large number of virtual subjects with a wide range of anthropometric variations (La Mattina et al., 2023). The impact force range predicted with our model has been previously validated against the range reported for experimental measurements (Laing and Robinovitch, 2009). Additionally, the model was able to accurately stratify fractured vs. non-fractured subjects (Bhattacharya et al., 2019). Another relevant aspect is computational time. In this work, around 7000 FE simulations were run for each realisation, and including soft tissues would be prohibitive in the framework of an *In Silico* Trial. On a similar point, the accuracy reported for our FE models is slightly lower compared with other non-linear explicit models available (Fleps et al., 2019; Koivumäki et al., 2012). In our experiments, fracture propagated to complete failure in a few milliseconds, with nearly perfect linearity on the force–displacement and force-strain curves (Cristofolini et al., 2007). Adding non-linearity relaxes any eventual imprecision in boundary conditions and constitutive equation, thanks to the increased order of the model; however, additional data is needed to train the missing parameters of the more complex constitutive equation. Therefore, we chose a simpler entirely mechanistic model, that provided sufficient accuracy, fully identified with measured quantities or literature values.

Another limitation of this study is the assumption that material properties of the femur did not vary over time, i.e., no osteoporosis progression was simulated. While this could be easily added to the simulation, we assumed that a patient to whom a hip protector was prescribed would most likely also be treated with anti-resorptive drugs, which slow down or stop the progression of the disease. Preliminary simulations assuming typical bone resorption rates produced identical conclusions on the efficacy of hip protectors.

Lastly, hip protectors were modelled empirically using an attenuation coefficient. Therefore, we did not model the potential inefficacy due to, for example, mispositioning of the device or deterioration. Another simplification is that compliance was independent of the device attenuation coefficient. In clinical settings, bulky devices (typically more effective due to their higher attenuation capacity) may be poorly accepted by patients and therefore be linked with lower compliance. However, technological innovation is producing new solutions with better ratios between size and attenuation.

The potential of this *In Silico* trial technology includes the possibility to test and compare different interventions or their combination, optimise treatment strategies on the same patients, which by definition would be impossible in experimental studies, improve clinical trial design and drug development. Using the same virtual patient as a control for itself is an important advantage of these methodologies. This provides an excellent ability to detect change, even when the model has high bio-fidelity, and accounts for a wide range of inter-subject variability factors.

In conclusion, an *In Silico* trial methodology (*BoneStrength*) was developed for the prediction of hip fracture incidence in large cohorts of virtual patients, and its first application was presented for assessing the effectiveness of hip protectors. Our results confirm that hip protectors can be highly effective, as far as compliance remains high. The same approach can be used to explore a number of clinically relevant questions on the design of clinical studies and provide insights on the efficacy of various types of physical and pharmacological interventions, for

which a clinical study is complex, too expensive, or simply impossible.

5. Open Access data

The following Open Access Data are linked to this manuscript: https://doi.org/10.6092/unibo/amsacta/7888.

Funding

This study was supported by the European Commission through the H2020 project "In Silico World: Lowering barriers to ubiquitous adoption of In Silico Trials" (topic SC1-DTH-06-2020, grant ID 101016503).

CRediT authorship contribution statement

Sara Oliviero: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antonino A. La Mattina:** Writing – review & editing, Software, Methodology, Investigation, Data curation, Conceptualization. **Giacomo Savelli:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **Marco Viceconti:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge the CINECA awards under ISCRA and PRACE-ICEI initiatives, for the availability of High-Performance Computing resources and support. We acknowledge the support of the H2020 project "CompBioMed2: A Centre of Excellence in Computational Biomedicine" (topic INFRAEDI-02-2018, grant ID 823712) that provided expertise on the In Silico Trial code and computational efficiency.

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