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Review Article

Digital Twins: A Futuristic Artificial Intelligence Methodology for Design and Analysis of Clinical Trials

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Abstract

This paper introduces the recently-proposed clinical trial design known as "*digital twins*". This design utilizes a single arm where all patients receive the experimental treatment. A digital twin of each patient is constructed by artificial intelligence methods from thousands of real-world data records, physiologic and molecular characteristics and the patient's baseline data. Presumably the only difference between the patient on the clinical trial and his/her digital twin is the experimental treatment. A matched pair analysis is now performed comparing each patient's outcome with that of the digital twin. Several methods of analysis are presented. The role of digital twin methodology in drug development is discussed including the potential of its use as a pivotal trial for drug approval.

Introduction

The U.S. Food and Drug Administration (FDA) issued a discussion paper on the use of artificial intelligence and machine learning (AI/ML) in drug and biologic development [1]. The paper indicates that FDA is expecting AI/ML to be used in molecule design, protocol writing, patient and site selection, adherence, clinical endpoint assessment, etc.

One interesting item is the notion of digital twin design and analysis. Cosmologists claim that each of us has an exact twin somewhere in the multiverse, but FDA is expecting that digital twins of clinical trial patients to be created *in silico* and used in analysis. FDA envisions a one-arm trial with all patients receiving the experimental treatment. Using real world data (RWD) from multiple sources such as electronic health records, medical claims, registries, etc. and physiological and molecular process models AI/ML can predict what the patient outcome would be had the patient not received treatment. Data analysis would consider the differences between observed and digital twin measures for efficacy and safety endpoints.

Background

Several researchers have already begun to work in this area. Laubenbacher, Sluka and Glazier indicate that medical digital twins are already being used in in conjunction with patient characteristics in real time to monitor insulin requirements and drive an implanted pump and to optimize heart surgeries [2]. They suggest that digital twins might someday be essential in developing treatments for highly transmissible viral infections such as SARS-Cov-2.

In the area of clinical trials, the European Medicines Agency has recently issued a document indicating that they are considering

a prognostic covariate adjustment model (PROCOVA ™). that has some resemblance to digital twins [3]. For each patient in a clinical trial this method of covariate adjustment adds a prognostic score as a covariate in a trial where patients receive experimental treatment on one arm while the control arm consists of patients receiving control treatment on previous trials. The prognostic score is derived from patient characteristics and RWD by AI/ML. It indicates the relative outcome of a patient on the control treatment. The prognostic score is added to patient baseline covariates to adjust the primary efficacy endpoint in the experimental treatment group. This method aims to reduce sample size and increase precision in estimation.

Schuler, Walsh and Hall et al describe a procedure similar to PROCOVA which they apply to a clinical trial for Alzheimer's Disease [4]. They demonstrate statistical properties such as Type I error control, asymptotic variance, and potential sample size reduction.

The Digital Twin Clinical Trial

The digital twin trial envisioned by FDA is a matched pair design. There is only one arm and all patients on that arm will receive experimental treatment. This would not be a randomized trial, but enrollment might be easier than in a two-arm trial where a potential patient would have only a 50% chance of receiving experimental treatment. Each patient will be compared to his/her digital twin. AI/ML would be used to follow a digital patient with same physiology, molecular structure, health history and baseline variables. This digital twin patient will be constructed from scanning thousands of electronic health records, medical claims, registries etc. The only difference between the patient and his/her twin would be the experimental treatment taken by the enrolled patient.

If the primary clinical endpoint is dichotomous, the matched pair analysis with the 2x2 table showing the agreement and disagreement between pairs would be applied [5]. If the endpoint is numerical, including change scores, the common test of the hypothesis that the mean difference is zero would be utilized. For a time-to-event analysis like survival time the digital twin is formed by following the twin longitudinally along with the patent. There could be a difference in event occurrence (censoring). Several time-to-event methods for paired times including possibility of censoring exist [6,7]. There is also the possibility that the emerging methodology of generalized pairwise comparisons could be used to score differences on paired data [8].

Similar analyses could be applied to safety data.

Evaluation

It is not surprising that digital twin methodology would be proposed at this time. There is a push among all regulatory agencies to use novel clinical trial design and analysis methods. At the same time an interest in employing AI/ML and real-world data (RWD) has appeared. The digital twin trial is not a randomized trial and, thus, its immediate use might be for Phase II trials and post-market trials, For the latter, this will be the first time for patients not eligible for the pivotal trial such as diabetics, pregnant women, patients taking steroids, etc. could receive the approved drug. Such a patient is not often interested in enrolling in a two-arm trial. For drugs receiving accelerated approval, this methodology could be used in the post-approval trial commitment. It is often difficult to get patients to enroll in these required post-approval trials because patients can now receive the approved drug from their community physician and would want to avoid the possibly of being randomized to placebo or standard of care.

Digital twins might be useful in making a go/no go decision for a new drug that has had a favorable safety profile and shown some evidence of efficacy in early phase II trials. Sponsors could simulate clinical trials with a range of outcomes for patients taking the treatment and compare with digital twins.

Many researchers will be dismissive of the digital twin design claiming that it is merely a glorified historical control trial. It is not likely that regulators would approve a treatment where the pivotal trial is digital twin. Much has been written of the many inferential problems with RWD [9,10]. Researchers have already reported problems in trying to replicate clinical trial results with RWD [11]. Also, there may be challenges to the way the AI/ML constructed the digital twin. Sponsors could have chosen digital twin methodologies and data sources most likely to show a favorable outcome for the experimental drug. The huge pool of data to construct the digital twin changes every minute making it difficult to evaluate or standardize.

The proportional hazards assumption in time to event regression analysis has long been problematic [12]. Several promising alternatives have been proposed, namely restricted mean survival time [13] and "*win statistics*" [8, 14]. In hypothesis testing, Bayes factor has been proposed as an alternative to the much-faulted p-value [15]. If these methods are presented at all it is as supportive evidence of efficacy and/or safety of experimental treatments. Of course, such results are usually only presented if they yield positive results for the experimental treatment. It is likely that digital twin methodology will join the ranks of these worthy methodologies.

Conclusion

Digital twin methodology is a creative and interesting entry in novel design and analysis methods for clinical trials. It is likely to find its way into early phase and post market trials but we are not likely to see the digital twins design as a pivotal trial any time soon.

Acknowledgement

None.

Conflict of Interest

None.

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