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Synthetic Control Arms Data Driven by AI: A Viable Alternative to Placebo Cohorts in Comparative Clinical Studies?

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INTRODUCTION

Randomised controlled trials (RCTs) with placebo controls are a cornerstone of clinical research. Although regulatory bodies such as the EMA and FDA do not mandate active treatment comparisons, placebo-controlled trials frequently struggle to demonstrate superiority over the standard of care (SoC) in Health Technology Assessments (HTA). Similarly, single-arm trials in oncology often face these same hurdles, posing significant risks to the value recognition of innovative therapies.

Artificial intelligence (AI) offers promising solutions to these challenges, especially through the development of synthetic control arms (SCAs). Digital twins are developed using historical patient data, periodical measurements, and machine learning algorithms to create virtual models of patients that mimic physiological and behavioral patterns. Retrospective analysis of real-word data in the form of historical SCAs have been used to support regulatory applications for nearly 50 years. However, traditional SCAs face criticism due to the limitations of manual analyses, which can impact their robustness and acceptance.

OBJECTIVES

This research examines the current use of AI-driven SCAs in diabetes and evaluates the limitations of non-AI-driven SCAs in oncology. The aim is to assess the feasibility and reliability of AI-driven approaches and to explore their potential in supplementing or replacing placebo cohorts with digital comparative evidence for HTA.

METHODS

Three validation studies (NCT04203823, NCT05313594, NCT05181449) evaluating the effectiveness of digital twins in diabetes and nutrition-related diseases were identified and reviewed. Additionally, the HTA reports by the French Haute Autorité de Santé (HAS) for blinatumomab and avelumab were analyzed to extract insights on the use and robustness of the SCAs in their data packages.

RESULTS

Digital twins

The three validation studies are detailed in Table 1. Of these studies, two have been completed; however, only one (NCT04203823) had published results at the time of this review. As summarized in Table 2, the digital twin model demonstrated effectiveness in predicting optimized therapy and meal settings that minimized adverse events and maintained patients' glucose levels within the normal range for a substantial portion of the study duration.

Trial	Status (start-end date)	Indication	Intervention	Objective	Location
NCT04203823	Completed, results posted (Jul 20-Jan 22)	Type 1 diabetes	Digital twin – Prediction algorithm on optimal insulin delivery and meal timing and content	Test the safety and effectiveness of the algorithm's recommendations	12 sites
NCT05313594	Completed (Mar 22-Jun 22)	Nutrition-related diseases (healthy volunteers)	Digital twin - Prediction algorithm on triglyceride and glucose response following meal challenge	Validate and improve the accuracy of the predictions	1 site
NCT05181449	Active (Feb 22-Jul 2025)	Type 2 diabetes	Digital twin - Prediction algorithm on glucose response following precision nutritional, activity and sleep guidance	Test the effectiveness of the algorithm's recommendations vs. usual care in reducing glucose levels	1 site

Table 1. Description of digital twins' validation studies

	Cohort A: Insulin delivery	Cohort B: Meal prediction
Number of patients enrolled	54	72
Outcome measures (measured over ~3.5 months)		
Number of severe hypoglycemic event	0	0
Number of diabetic ketoacidosis	0	0
Percentage of time in euglycemia	70.5%	77%

Table 2. NCT04203823 study results

Historical SCA

Blinatumomab received EMA approval in 2015 for the treatment of B-cell precursor acute lymphoblastic leukemia (B+ ALL), and avelumab was approved in 2017 for metastatic Merkel cell carcinoma (MCC). HAS evaluated these therapies in 2016 and 2018, respectively. Due to limited comparative data available at the time of assessment, manufacturers included SCA data in their evidence packages. Commentary from HAS on the robustness and limitations of these SCAs is provided in Figure 1.

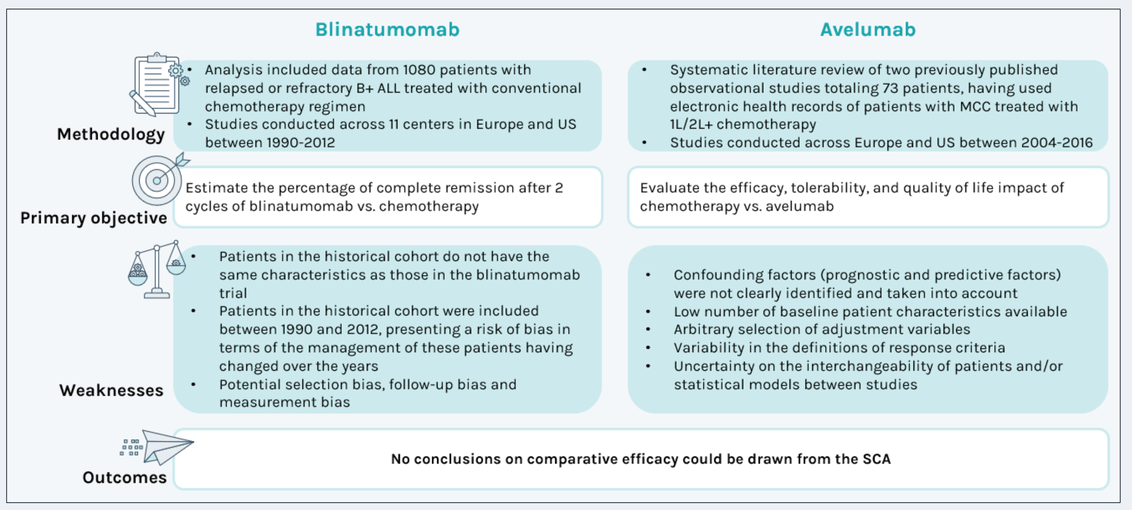

Figure 1. HAS HTA assessment outcomes of blinatumomab and avelumab

CONCLUSION

The review of three validation studies (NCT04203823, NCT05313594, NCT05181449) highlights digital twins as promising tools for disease management, especially in nutrition-related and behavioral conditions. These studies demonstrate the potential of digital twins to address challenges in real-time monitoring, dynamic analysis, and personalized treatment. However, limitations exist: the lack of comparative outcomes with usual care in NCT04203823 and NCT05313594 makes it difficult to assess the superiority of digital twins. The upcoming results of NCT05181449 will be important for further evaluating their reliability in managing diabetes.

This evidence supports digital twins as viable solutions in areas requiring continuous monitoring and tailored interventions, and it highlights their potential for expansion into other therapeutic domains. Moreover, the main limitations identified by HAS in the HTA assessments of blinatumomab and avelumab—such as retrospective matching and confounding bias—suggest areas where AI-driven analytics could bring improvements. The scalability and precision of AI-driven SCAs offer a promising alternative for generating robust comparative data, particularly in complex and data-intensive fields like oncology.

Together, these findings suggest that AI-driven methodologies for digital comparative efficacy data hold significant promise for enhancing acceptability in regulatory and HTA contexts. Additionally, they could help address ethical and recruitment challenges in placebo-controlled trials, especially for rare or severe diseases, by enabling robust sample sizes and reducing reliance on placebo cohorts. Nonetheless, improving data quality, establishing standards, and developing clear guidelines will be essential to enhance confidence and facilitate broader adoption of these approaches in the future.

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