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Generative Artificial Intelligence Augmentation of a Clinical Trial of a Dermo-cosmetic Intervention for Acne Remission Maintenance

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ABSTRACT

Background: A practical application of artificial intelligence (AI) in healthcare is to generate artificial datasets that capture the characteristics of a real source dataset without exposing protected health information. This approach is particularly relevant to research settings where recruitment and long-term follow-up are barriers to generating robust clinical evidence.

Objective: To describe the protocol of a study incorporating augmented patient datasets to assess the efficacy of a dermo-cosmetic product (Cleanance Comedomed+®) in maintaining acne remission after discontinuation of oral isotretinoin.

Methods: In a randomized, placebo-controlled, blinded clinical trial, patients will receive the dermo-cosmetic product or placebo for up to 12 months. Study outcomes are the number of observed relapses and time to first relapse. To overcome recruitment constraints and reach the 400 patients required to ensure sufficient precision for a time-dependent event criterion, a cohort augmentation strategy using artificial data is implemented. The technology relies on generative models of the Riemannian Hamiltonian Variational Autoencoder type, which learn a compact and geometrically structured latent representation of real clinical data. Generation of artificial patients will occur iteratively, and the initial dataset will be progressively enriched as new real inclusions become available. Reliability of generated data will be assessed and validated through human oversight using quantitative and qualitative metrics covering 4 dimensions: (1) statistical fidelity; (2) diversity and utility; (3) confidentiality; and (4) clinical plausibility.

Discussion and Conclusion: Structured integration of artificial data into this clinical trial illustrates the potential of generative AI as a methodological tool complementing conventional approaches in clinical research.

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INTRODUCTION

Generative artificial intelligence (AI) is increasingly being adopted in healthcare settings to accelerate innovation.[1] Realistic artificial datasets can be generated to capture the characteristics of a real source dataset (distributions, non-linear relationships, noise) without exposing protected health information.[2,3] Artificial data can overcome patient recruitment difficulties and mitigate the impact of prolonged follow-up and low-frequency or stochastic events already observed in the real dataset by stabilizing their statistical representation, while providing statistical power equivalent to that obtained with exclusively real data. Probabilistic and generative models have been shown to faithfully reproduce not only marginal distributions, but also multivariate dependencies and certain clinical trajectories observed in limited datasets.[3-7]

The medicalization of dermo-cosmetic products requires the production of robust, comparative, and reproducible clinical evidence. In the setting of recalcitrant moderate to severe acne, systemic treatment with oral isotretinoin remains the therapeutic gold standard.[8,9] However, a substantial proportion of patients relapse after treatment discontinuation,[10,11] underscoring the need to develop effective strategies for the post-isotretinoin maintenance phase. As reasons for relapse are myriad and individual,[11,12] demonstrating the efficacy of dermo-cosmetic

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solutions in this context requires lengthy comparative clinical trials with large sample sizes, which are often difficult to recruit.

Here, we describe an innovative methodology intended to address a major bottleneck in dermatological research: the difficulty of recruiting large patient cohorts for long-term follow-up studies. This approach is illustrated by the protocol of a study designed to assess maintenance treatment in post-isotretinoin patients. Notably, integration of blinded clinical validation by expert dermatologists aims to ensure that artificial patient profiles are medically indistinguishable from real patients, thereby bridging the gap between statistical fidelity and clinical reality. Importantly, the protocol recognizes that the use of artificial data in clinical research is interpreted as a methodological support tool rather than as a substitute for real-world clinical evidence, and its outputs must be contextualized within a robust clinical and regulatory framework.

MATERIALS AND METHODS

Clinical Trial Design

A randomized, placebo-controlled, blinded clinical trial has been designed to evaluate the efficacy of a dermo-cosmetic product (Cleanance Comedomed+®) in maintaining acne remission after discontinuation of oral isotretinoin. The emulsion contains milk thistle *Silybum marianum* fruit extract and niacinamide, for daily facial use by adolescents and young adults with acne-prone skin. Under strict inclusion criteria, patients are to be randomized into 2 parallel arms to receive the dermo-cosmetic product or placebo (excipient formulation). Treatment duration is planned for up to 12 months. Study outcomes include the number of observed relapses and time to first relapse. Patients with acne relapse will be withdrawn. Acne relapse is defined as investigator-confirmed clinical worsening requiring treatment initiation leading to patient withdrawal, ensuring consistency with routine dermatological practice. To limit inter-observer variability, investigators are to follow harmonized relapse assessment criteria predefined in the study protocol. To ensure compliance with ethical standards and participant rights, the clinical study protocol has been thoroughly reviewed and approved by ethics committees. Study participants will be provided with the necessary information regarding the use of AI on their pseudonymized data.

The statistical power calculation indicated the need to include nearly 400 patients to ensure sufficient precision for a time-dependent event criterion. However, recruitment constraints (inclusion window limited to about 6 months, 1-year follow-up burden, multicenter logistics) were expected to restrict enrollment to around 100 patients, potentially compromising the statistical validity of the study and exposing it to an underpowering risk. Innovative solutions integrating AI were therefore considered. The approach presented here offers a dual advantage: securing the statistical power necessary to detect rare relapse events while minimizing the ethical burden of enrolling additional real patients under placebo-controlled conditions.

Methodological Integration of Artificial Data

To ensure scientific feasibility of the trial without compromising its methodological rigor, a cohort augmentation strategy using artificial data is implemented. The generative modeling technology was developed by BOTdesign (Toulouse, France) and operationalized within the ORIGA platform. It relies on generative models of the Riemannian Hamiltonian Variational Autoencoder (RHVAE) type, which learn a compact and geometrically structured latent representation of real clinical data.[6,7] Unlike classical generative approaches based on direct sampling from a prior in a Euclidean latent space, RHVAEs model the latent space as a Riemannian manifold whose metric is learned from observed data, enabling improved capture of high-information-density regions.

The geometric structuring enables generation of new samples with statistical and clinical characteristics close to those of real patients, without reproducing original individual observations or limiting generation to simple interpolation, thereby contributing to both plausibility and confidentiality. This approach, described as particularly suited to small real cohorts, is relevant in trials with limited sample sizes and time-dependent event criteria, where interindividual variability and censoring (premature withdrawals, relapse leading to discontinuation) can strongly affect statistical power. By employing RHVAE-based models, the study aims to move beyond traditional data interpolation to capture the high-dimensional complexity and non-linear relationships inherent in dermatological clinical trajectories.

Notably, artificial data are used to augment statistical power and enrich patient-level variability for time-to-event modeling under censoring, while preserving the structure learned from real patients. Artificial data do not replace, but complement, real patient observations in primary efficacy or safety analyses.

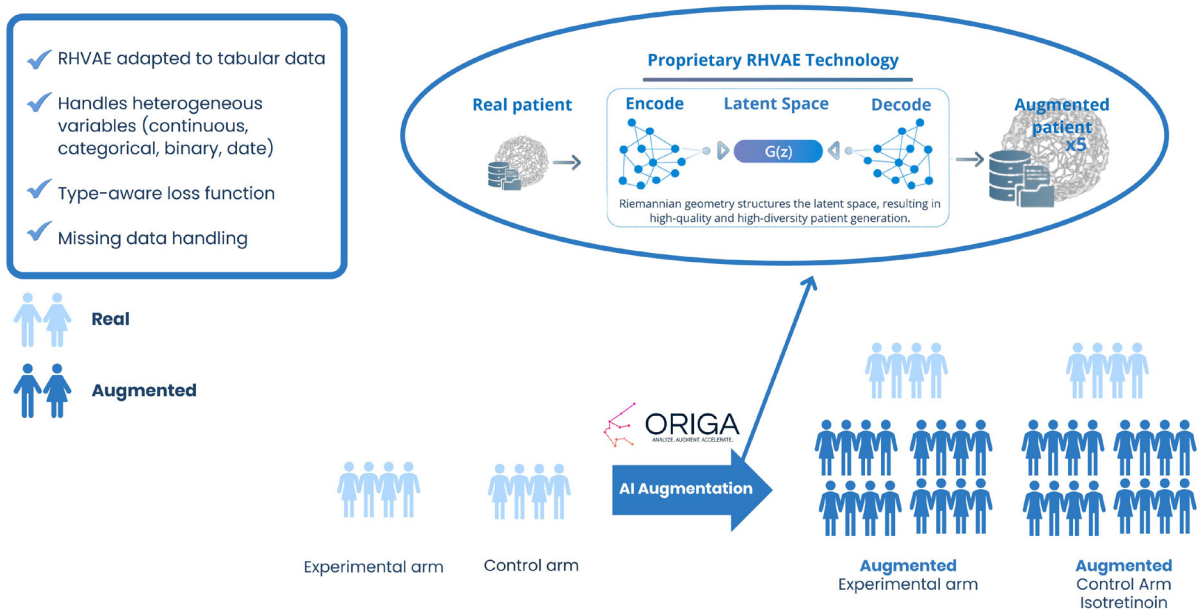
Integration Procedure Within the Trial Design

Methodologically, integration of artificial data within the trial is designed as a controlled, balanced, and documented augmentation of both treatment arms (Cleanance Comedomed+® and placebo). In line with the operational organization of the trial, a limited number of real patients are to be enrolled (approximately 50 per arm at initiation of the strategy) according to observed recruitment pace and field constraints; data from these patients will form the initial learning base. For each real patient, 5 artificial patients are to be generated within the corresponding arm (treated or control), resulting in 2 augmented cohorts while preserving the original randomized comparison and avoiding disproportionate amplification of 1 group (Figure 1).

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FIGURE 1. Use of ORIGA's technology in clinical study design.



Generation of artificial patients is to be carried out iteratively during the study, following an agile project management framework. Once minimum quality and completeness criteria are met, an initial dataset provided to BOTdesign will be progressively enriched as new real inclusions become available. At each stage, the RHVAE model will be adapted using the expanded real database and subsequently used to produce updated artificial cohorts that progressively integrate observed interindividual variability. This adaptive approach aims to limit biases associated with small initial samples, reduce the risk of distributional drift between artificial data and the recruited population, and maintain clinical representativeness over time. The strategy preserves the initial randomization scheme (artificial patients being attached to already randomized arms), maintains balance of clinical covariates by design and, through post-hoc checks, avoids distortion of group comparisons and supports the statistical power of final analyses.

Statistical, Clinical, and Regulatory Validation

Emerging requirements of the European regulatory framework and governance principles for AI use in healthcare require that the reliability of generated data be assessed and validated through human oversight using quantitative and qualitative metrics covering 4 dimensions: (1) statistical fidelity; (2) diversity and utility; (3) confidentiality; and (4) clinical plausibility. From the setup phase, BOTdesign's prerequisites are jointly reviewed, test datasets are transmitted to verify technical feasibility, and artificial data deliveries are accompanied by detailed expert reports documenting data quality beyond the mere provision of datasets. Pierre Fabre experts (statistician, AI specialist) contribute to defining acceptance thresholds and interpreting indicators. A dermatologist-based validation methodology is defined in collaboration with BOTdesign to complement quantitative metrics with blinded clinical evaluation.

Within BOTdesign's AI generator, statistical fidelity is assessed using metrics established in the artificial data validation literature.[4,13] Wasserstein distances are calculated variable by variable to quantify the proximity of marginal distributions between real and artificial data, then extended to multivariate analyses to evaluate the preservation of structural relationships among clinical variables. Conditional analyses are planned within clinically relevant subgroups (eg, by initial severity, follow-up characteristics, or risk profiles) to verify that fidelity is maintained not only globally but also within strata critical for clinical interpretation. Statistical moments up to the fourth order are compared in order to capture mean and variance as well as skewness and kurtosis. All indicators must show deviation below 5% compared with real data. This constraint aims to ensure that augmentation does not artificially alter the data structure underlying analyses, particularly those related to relapse timing.

Diversity and utility are assessed to verify that the generator does not merely reproduce or memorize original data and avoids collapse. The width of interquartile ranges and 5% to 95% intervals is compared between real and artificial data, with generated data expected to show wider intervals, interpreted as

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evidence of capacity to produce new profiles while remaining within a plausible clinical space. A collapse test across successive generations complements this analysis, aiming to detect any progressive impoverishment of variability during iterative adaptations of the model. Inter-iteration stability is monitored to ensure that enrichment of the real base and model adaptation does not introduce uncontrolled drifts.

Confidentiality is assessed using re-identification risk metrics inspired by the literature.[14] A real observation is considered sufficiently protected if at least 1 artificial data point is closer to it than its own reconstruction by the model. This operational criterion is used to indicate the absence of trivial memorization and the ability of the model to generate plausible synthetic neighbors without replicating original observations. At least 50% of observations are required to meet this criterion, complemented by additional analyses of information leakage or differential privacy-inspired metrics to document a level of protection compatible with confidentiality requirements.

Finally, clinical plausibility of artificial patients is assessed by expert dermatologists through a blinded procedure. Evaluation datasets mix real and artificial profiles, with the proportion of artificial data randomly drawn between 20% and 80% for each assessment batch, and the remainder consisting of real patient data. Practitioners are asked to assess whether profiles are clinically coherent and distinguishable, focusing on intra-patient consistency, plausibility of trajectories across visits, and compatibility of timelines and events. An error rate approaching random classification is considered an indicator of satisfactory clinical indistinguishability, suggesting that artificial data reproduce plausible patient profiles without readily detectable artifacts. This step represents a key translational bridge between AI and clinical dermatology, ensuring that synthetic data are not only statistically valid but also clinically interpretable and coherent with real-life patient trajectories.

DISCUSSION AND CONCLUSION

This study was conducted in Europe, where the integration of artificial data into clinical research is an emerging topic. Similar to Europe, the United States has also established a regulatory framework guiding the use of AI in healthcare.[15-17] This parallel evolution highlights the importance of situating methodological innovations, such as augmented clinical trials, within both European and American regulatory contexts.

The structured integration of artificial data into this clinical trial illustrates the potential of generative AI as a methodological tool complementing conventional approaches in clinical research, particularly when operational constraints limit real sample size while, concurrently, the nature of the endpoint (relapse), its random occurrence, and follow-up duration require large cohorts. Beyond operational benefits related to recruitment feasibility and timeline optimization, this strategy addresses scientific challenges (statistical power, stability of estimates), ethical considerations (limiting exposure of additional real patients while maintaining balanced augmentation of both arms), and regulatory expectations (traceability, human oversight, validation across fidelity, diversity, confidentiality, and plausibility dimensions), while maintaining a high level of methodological rigor. This approach contributes to the emergence of augmented clinical trial paradigms, particularly relevant in dermo-cosmetic research and, more broadly, in fields where recruitment and long-term follow-up represent major barriers to generating robust clinical evidence. Importantly, conclusions drawn from augmented datasets should always be interpreted in conjunction with real patient data and should not be used in isolation to support clinical or therapeutic recommendations.

DISCLOSURES

Marco Ardigò has been a consultant and/or speaker and has participated in advisory boards for Almirall, Cantabria, Incyte, Johnson and Johnson, Kyowa Kirin, L'Oreal, Pierre Fabre, Recordati Rare Diseases, SunPharma and Takeda. Luigi Gargiulo has been a consultant and/or speaker and has participated in advisory boards for AbbVie, Almirall, Amgen, BMS, Eli Lilly, Galderma, Incyte, Johnson and Johnson, Novartis, Pfizer, Pierre Fabre, Sanofi, and UCB Pharma. Raphael Fontaine is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Olivier Thuillart is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Jean-Louis Fraysse is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Adeline Bacquey is an employee of Pierre Fabre Laboratories who sponsored the study. Pauline Lacoste is an employee of Pierre Fabre Laboratories who sponsored the study. Stéphanie Allassonnière's research is partially funded by the French National Research Agency through the AI Clusters program (grant ANR-21-RHUS-0012) and by the European Union under the ERC Synergy programme (2023–2030), grant agreement No. 101071601 (OCEAN). Aline Stennevin is an employee of Pierre Fabre Laboratories who sponsored the study. Gautier Doat is an employee of Pierre Fabre Laboratories who sponsored the study.

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