From Data to Patient Access: Enabling Synthetic Control Arms Using Real World and Synthetic Data for Trials and HTA decision-making

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EXECUTIVE SUMMARY

Artificial intelligence (AI) is revolutionizing clinical research and health data management, particularly through synthetic control arms (SCAs) and hybrid designs, which address challenges in rare diseases, pediatric trials, and underrepresented populations. These AI-driven approaches enhance trial efficiency, inclusivity, and predictive power while reducing patient exposure to placebo or suboptimal treatments.

However, adoption depends on regulatory alignment and methodological validation. While frameworks exist at the FDA and EMA levels, further guidance is needed at the EU HTA and national levels, including in France, where ongoing initiatives lack clarity on HTA integration.

To accelerate adoption, the paper proposes **three key recommendations**.

By fostering structured validation and early regulatory dialogue, AI can reduce uncertainty in decision-making, shorten development timelines, and accelerate patient access to innovative therapies—positioning France and Europe as leaders in ethical AI-driven healthcare innovation.

Artificial Intelligence as a Strategic Lever for Clinical Research and Patient Access

The integration of artificial intelligence (AI) into clinical research and health data management represents a major shift in the landscape of biomedical innovation. The thematic workshop organized during the ARIIS 15th anniversary — bringing together academic researchers, industry stakeholders, public institutions, and patient organizations — provided a timely forum to collectively examine how AI is reshaping clinical research and the use of health data.

AI-driven methodologies offer substantial added value by enabling the investigation of clinical questions that are difficult or impossible to address using conventional approaches, particularly when randomized controlled trials are not feasible. These approaches are also increasingly used to complement conventional trials by generating additional, context-relevant evidence.

Through the creation of virtual or augmented cohorts, AI opens new perspectives to improve the efficiency, inclusivity, and predictive power of clinical research. These tools can help overcome persistent challenges such as patient recruitment, high development costs, and lengthy timelines issues that are especially acute in rare diseases, pediatric populations, slow-progressing conditions, and groups traditionally underrepresented in clinical trials.

Beyond operational gains, ethically designed AI-based virtual cohorts also support a more patient-centered approach to research. By limiting exposure to treatments unlikely to be beneficial and focusing on patients most likely to respond, they enhance both ethical rigor and scientific relevance.

Finally, these methodological advances carry strategic implications. France and Europe have an opportunity to position themselves as leaders in the development, validation, and deployment of ethical, secure, and scientifically robust AI applications in health, particularly virtual cohorts, capable of translating innovation into tangible benefits for patients and healthcare systems.

Building Trust, Alignment, and Regulatory Confidence

Large-scale adoption of AI in clinical research depends first and foremost on trust — from regulators, Health Technology Assessment (HTA) bodies, clinicians, patients, and developers. Transparent, explainable, and validated AI methodologies can reinforce the robustness of evidence, support more efficient decision-making, and ultimately accelerate patient access to safe, effective, and innovative therapies.

Routine integration of AI-based approaches — including synthetic data generation and advanced real-world data analyses — into phase III clinical development requires close and sustained collaboration among European and French health authorities (EMA, ANSM, HAS), the FDA, patient representatives, clinical research experts, sponsors, and methodologists. Moving from experimentation to implementation requires convergence on a limited number of shared, high-impact objectives. As such, the French Health Innovation agency (AIS) and the French Clinical Research Infrastructure Network (F-CRIN) launch an initiative to financially support use cases to assess the level of evidence of new clinical research methodologies[1]. An international jury selected 16 projects which will help demonstrate the value of new tools and clinical research methodologies, thereby facilitating their adoption by the broader ecosystem and regulatory authorities[2].

This paper addresses two distinct methods: synthetic control arms and hybrid control arms (combining real and synthetic data). It distinguishes between their application as necessary alternatives when conventional randomized controls are not feasible, and their potential use as complementary for traditional control arms — while emphasizing that such approaches require prior validation through implementation in settings where designs can be compared.

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[1] ANR - **France 2030 : 16 lauréats pour évaluer le niveau de preuve des nouvelles méthodologies de recherche clinique – April 2026 - https://anr.fr/**

[2] https://anr.fr/fileadmin/documents/2026/CP-France2030-Laureats-AMI-NMRC-20260409.pdf

Two complementary priorities should therefore be pursued in parallel:

- **Identifying and prioritizing use cases** where synthetic data can meaningfully accelerate clinical trials, particularly in hard-to-recruit populations (children, elderly or frail patients, rare diseases, end-stage cancers, underrepresented groups) and slow-progressing diseases. In these contexts, synthetic arms may complement and enrich traditional approaches, and in some cases substitute for a conventional control arm when randomization is not feasible — provided this substitution is preceded by a validation phase in which both real and synthetic arms coexist.

- **Reinforcing shared methodological framework, including criteria** to assess the reliability, safety, and scientific relevance of these methods, enabling their acceptance by regulatory authorities and integration into HTA decisions. Guidelines have already been published at FDA and EMA levels and need to be defined at the EU HTA levels [3] [4] [5]

Toward a Structured National and European Framework

At the French level, the Ministry of Health and French Health Innovation agency (AIS) are engaged in developing methodological frameworks. However, the absence of an evolving HTA doctrine continues to limit industry engagement. At the European level, the EMA has initiated work on these new methodologies, while ongoing exchanges with the ANSM and HAS must now translate into concrete outcomes and framework, to strengthen France's attractiveness and sovereignty in clinical research.

In coordination with the EU recommandations, a key challenge remains how the national HTA will integrate these new forms of evidence into its assessments. Clarifying this trajectory is essential to provide industry stakeholders with the visibility needed to secure their investments.

Building on Existing Initiatives

This position paper builds on recent collaborative work carried out by the French Health Innovation Agency (AIS) and the French Clinical Research Infrastructure Network (F-CRIN). Over more than a year, the AIS–F-CRIN working group has explored a wide range of innovative methodological approaches, including external control arms, synthetic data, and modeling and

[3] GUIDANCE DOCUMENT
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products February 2023 - FDA-2022-D-2983

[4] ICH M15 guideline on general principles for model-informed drug development - Scientific guideline - EMA/CHMP/ICH/496426/2024

[5] Guiding principles of good AI practice in drug development -FDA -EMA – January 2026 https://www.fda.gov/media/189581/download

simulation [6] [7]. Together, these reports propose practical recommendations to support the dissemination and adoption of these approaches—particularly in silico simulations—as complementary evidence enhancing traditional clinical development strategies. They provide a strong foundation for the formulation of actionable and forward-looking recommendations. A follow-up to this work is the initiative to financially support use cases.

In parallel, other initiatives are contributing to structuring this emerging field [8]. For example, the SILICA Alliance is actively working on artificial health data, notably through the development of a shared glossary to foster a common understanding and by proposing a reference framework to support and scale the responsible use of artificial data across the ecosystem [9].

A Pragmatic Focus: Synthetic Control Arms as a Priority Entry Point

To translate ambition into action, this paper deliberately focuses on one priority use case: synthetic control arms (SCAs), which represent today's most operational entry point for integrating AI into clinical research. Four key levers are identified: acceptability and awareness-building, structured dialogue with authorities, financing models, and the development of concrete use cases.

Toward Collective and Progressive Learning: Acceptability, Trust, and Awareness: 3 recommendations

The development of SCAs must follow a logic of continuous learning, through progressive experimentation, and the establishment of a framework and of a network of academic experts.

The deployment of SCAs currently faces acceptability challenges stemming from perceived opacity of methods, heterogeneous practices, and the absence of a shared framework with no clear consensus at this stage on their role and current limitations. Building a trust framework is essential to demonstrate their value: reduced placebo exposure, accelerated trials, and

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[6] Taskforce AIS/F-CRIN "L'évolution des méthodologies d'essais cliniques : nouveaux outils, nouveaux usages et conditions de recours" Sous-groupe « Données » : « Pour l'utilisation des données de santé en vie réelle en recherche clinique Etat des lieux, analyse et recommandations » Mai 2024 https://www.fcrin.org/nouvelles-methodologies-en-recherche-clinique/livrables-et-avancement-des-travaux

[7] État d'avancement des évolutions méthodologiques en recherche clinique De la recherche expérimentale au suivi d'évaluation en phase d'usage courant GT AIS/F-CRIN « L'évolution des méthodologies d'essais cliniques : nouveaux outils, nouveaux usages et conditions de recours » Rapport Mai 2025 - https://www.fcrin.org/nouvelles-methodologies-en-recherche-clinique/livrables-et-avancement-des-travaux

[8] Données de santé artificielles : analyse et pistes de réflexion » Livre blanc coordonné par : Pr. ALLASSONNIÈRE Stéphanie Université Paris Cite & Dr. FRAYSSE Jean-Louis Botdesign. https://static.botdesign.net/docs/VF_Livre_blanc_Donn%C3%A9es_de_sant%C3%A9_artificielles-250424.pdf

[9] https://silica-asso.fr/

improved robustness of comparisons. This requires early scientific dialogue with decision makers, independent methodological validation, and sustained efforts to build awareness among clinicians and patients.

Recommendation 1 : To reconcile the positions of regulators and industry, one pragmatic approach would be to design clinical trial protocols incorporating three arms:

- a treatment arm composed of real patients;
- a control arm composed of real patients;
- an additional control arm consisting of synthetic patients, designed to validate the reliability and robustness of this virtual arm.

This validation phase — already approved in principle by French authorities and beyond — would allow industry to demonstrate the relevance of synthetic methods without jeopardizing trial integrity.

Recommendation 2 : A dedicated working group bringing together ariis, the SILICA Alliance, and industry representatives could further develop and propose this methodological framework, with the objective of encouraging regulatory authorities to accept to integrated a virtual control arm in the evaluation, even in the event of minor statistical discrepancies between the real and virtual control arms relative to the treatment arm.

Recommendation 3: establishing an independent academic trusted third party, supporting health authorities and HTA bodies in strengthening their expertise and sharing early advices on study-design, as new methodologies are deployed. This accredited academic community would be capable of providing scientific guidance, methodological standards, and independent validation.

Conclusion: Artificial Intelligence as an Enabler of Randomized Clinical Trials

AI-enabled approaches represent a powerful methodological enhancer, capable of improving the efficiency, feasibility, and ethical balance of clinical research. By optimizing trial design or even allowing feasibility, reducing unnecessary patient exposure to suboptimal or placebo treatments, and leveraging high-quality real-world and synthetic data, these approaches can mitigate patient risk while preserving scientific rigor. When appropriately framed, transparently validated, and used in complementarity with conventional methodologies, AI-supported tools offer a unique opportunity to reduce uncertainty for decision-makers, accelerate clinical development timelines, , and bring meaningful innovations to patients faster — without lowering evidentiary standards.

Achieving this requires a shared framework of trust, early dialogue with regulatory and HTA authorities, clear methodological expectations and the support of a trusted academic third-party — so that innovation and patient protection can advance hand in hand.

This document is the result of a collective effort by multiple stakeholders to foster discussion and advance recommendations on these new methodologies with decision-makers. It remains a work in progress, involving all actors across the ecosystem.

Acknowledgments: Camille Schurtz, Mathieu Robain – UNICANCER, Vincent Diebolt - F-Crin Inserm, Bertrand de Neuville - Heva Docaposte for their participation to ariis workshop and proofreading this manuscript. Thanks to all the participants of the ariis workshop on the 16th of September 2025: Severine Abramatic – CNCR, Bachra Balis – Pfizer, Clementine Body & Laetitia Gambotti – Agence de innovation en santé, Marc Bonneville – ariis, Nicolas Bruno & Marion Pinet – Novartis & ariis, Jennifer Bourland – L'Oréal, Arnaud De Guerra - Institut Santé Publique Inserm, Ségolène De Retz – Fondation ARCAD, Christophe Demonfaucon – France assos santé, François Depasse& Joffrey Ferriel – Stago diagnostic & ariis, Emmanuel Dequier – Direction Générale à la Recherche et l'Innovation – Ministère de l'enseignement supérieur et de la recherche, Annie Druet – Cabanac – Ipsen & ariis, Quentin Dufour – CNRS, Melina Gilberg – Amgen & ariis, Caroline Guillot – Plateforme des données de santé – HDH, Anne Kimmerling – Novonordisk & ariis, Gabriel KO – Biokortex, Yann-Mael Le douarin – Direction Générale à l'offre de soin – Ministère de la santé, Magali Léo – Moi patient, Anne Liaubet – Roche diagnostic & ariis, Felix Maillochaud – Bot design, Sebastien Mourey – Screenact, Jean-Philippe Plançon – Fondation des Maladies Rares, Anny Tirel – Seintinelles & Filière intelligence artificielle & Cancers, Christine Trilloux – F-Crin & Inserm, Jacques Vernin – Facophar santé & ariis