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EUCOPE representation
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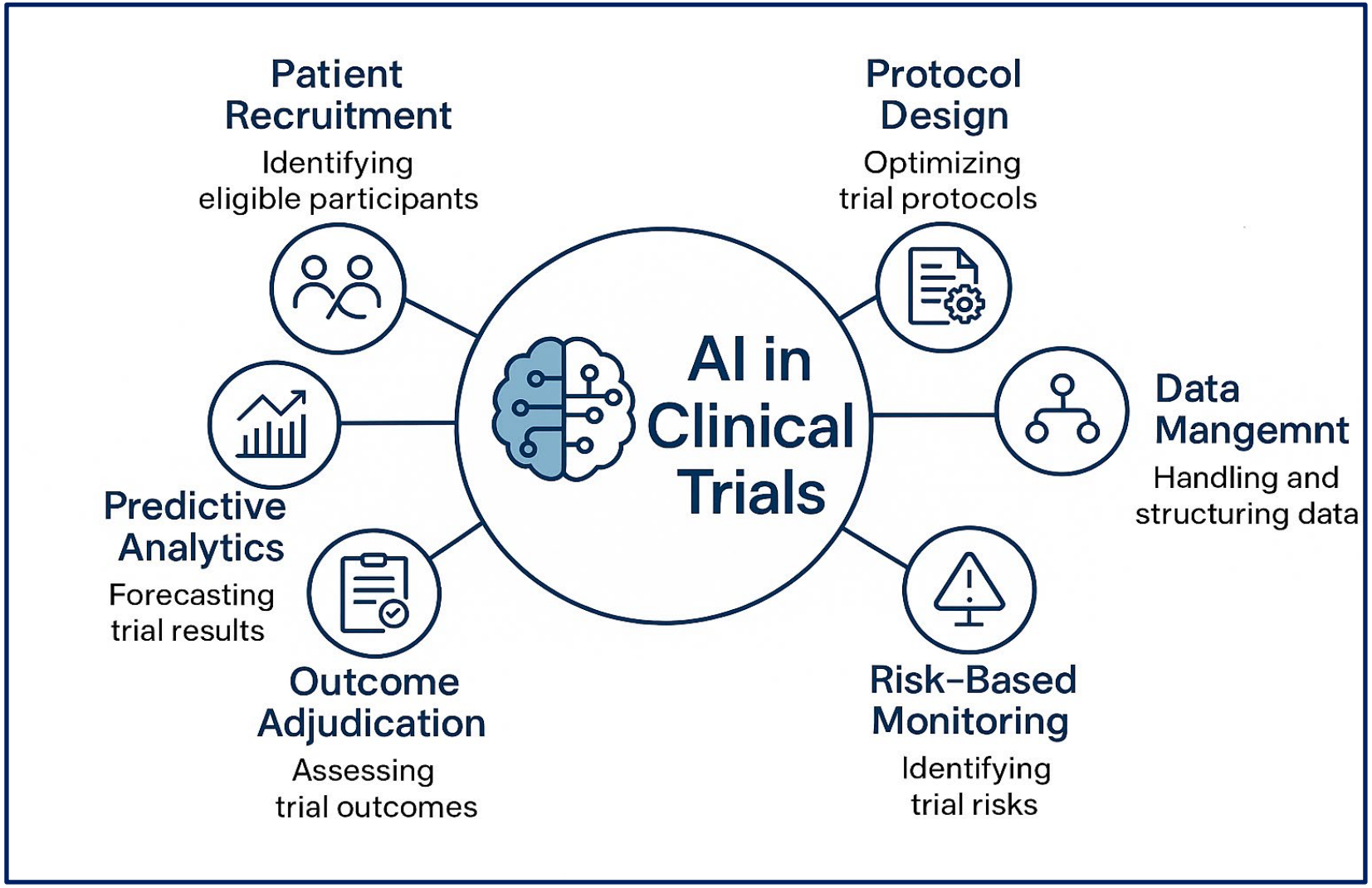
The views and opinions expressed in this presentation are those of the speaker in their capacity as a representative of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) and do not necessarily reflect the official policy or position of Sanofi. This presentation is for educational and informational purposes only and should not be construed as regulatory guidance or recommendations for specific regulatory submissions.

By leveraging AI in clinical trials, we can enhance efficiencies and innovation in clinical development plans

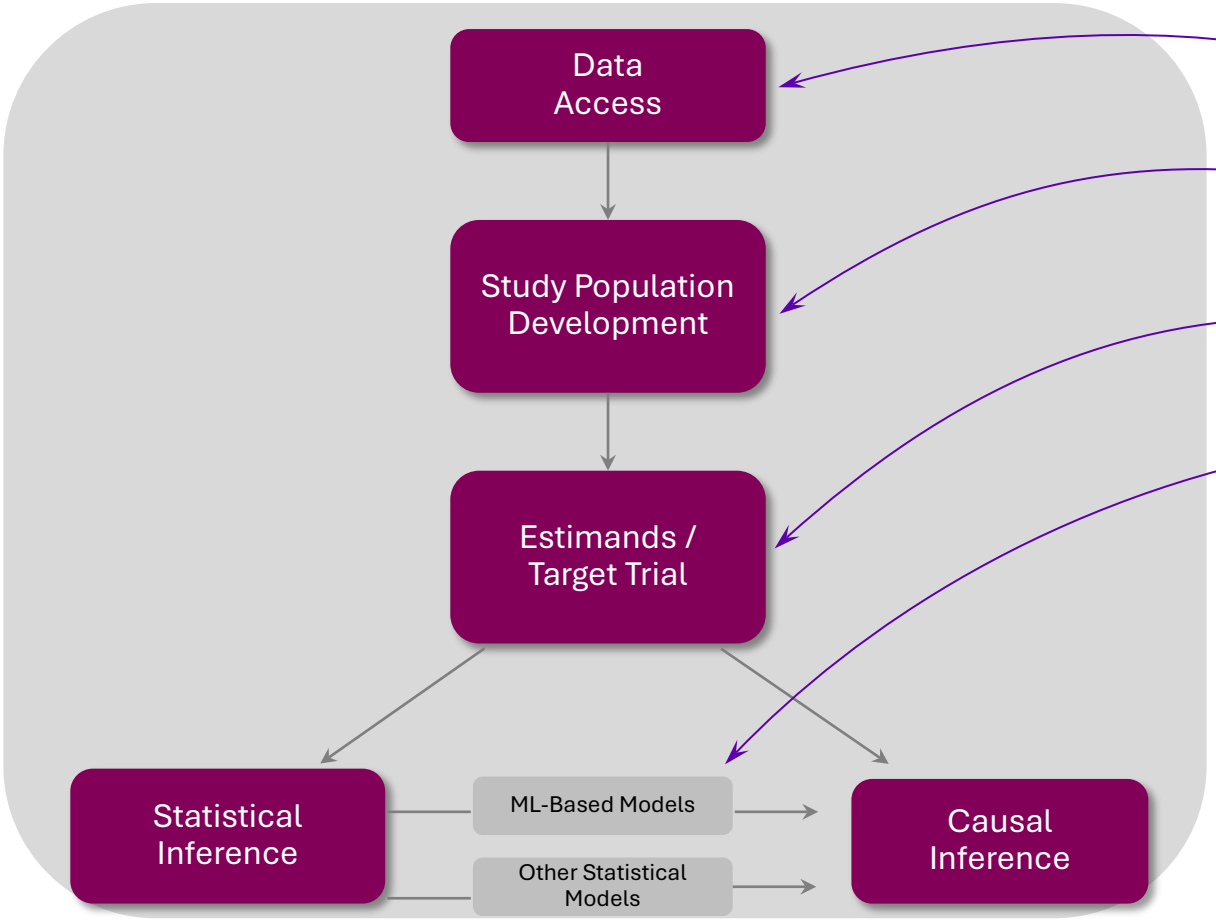


- Use of Artificial Intelligence (AI) in clinical trial within the context of evidence generation - AI used in the (clinical) dossier rather than automation and process efficacy.
- The opportunities of using AI in drug discovery and drug development are not part of this talk.

This presentation discusses methodological approaches and does not constitute regulatory advice. Case studies and examples are presented for educational purposes only. Regulatory acceptance of AI/ML methodologies may vary by jurisdiction and indication.

By leveraging AI in Non-Interventional studies, we can improve accuracy, scalability, and efficiency when dealing with complex observational data

Tasks of Evidence Generation



Potential of AI

Data Curation
- Harmonize diverse datasets and extract structured variables from clinical notes to improve data quality and completeness

Operationalize Endpoints
- Define and validate endpoints from real-world data to align definitions with past or conceptual RCTs

Confounder Identification
- Detection of confounders and latent structures to strengthen trial emulation and ensure causal identifiability criteria

Enhanced Estimation
- AI-driven methods to improve the outcome and propensity model estimation for robust causal inference (e.g., TMLE)

Status of AI

- Use of AI in data curation is well established
- Use to operationalize endpoints and confounder identification is emerging
- Enhanced estimation is established but the value is not yet clear

* Use of AI in Real World Evidence - this is within the context of evidence generation - AI used in the (clinical) dossier - rather than automation and process efficacy. The information contained in this presentation is confidential and proprietary. Any reproduction or distribution without written consent is prohibited. **References**: Cashin AG, Hansford HJ, Hernán MA, Swanson SA, Lee H, Jones MD, Dahabreh IJ, Dickerman BA, Egger M, Garcia-Albeniz X, Golub RM, Islam N, Lodi S, Moreno-Betancur M, Pearson S-A, Schneeweiss S, Sharp MK, Sterne JAC, Stuart EA, McAuley JH. Transparent Reporting of Observational Studies Emulating a Target Trial: The TARGET Statement. JAMA 2025 (in press). (also BMJ 2025 390: e087179-e087179). Hernán MA, Dahabreh IJ, Dickerman BA, Swanson SA. The target trial framework for causal inference from observational data: Why and when is it helpful? Annals of Internal Medicine 2025; 178:402-407.

AI/ML has a clear potential to be used in Target Trial Emulation and Causal Inference : Use Case and Potential Applications – Aligned with the JAMA-TARGET Statement

Background and Rationale

- Therapy for cGVHD
- High unmet need
- High rate of failure with available agents

Causal Question

- Difference in ORR at week 26 in this population with an investigational agent vs. BAT

Rationale for RWE-based evaluation

- Investigational agent approved in a country with use in clinical practice, enabling real-world data collection
- Faster generation of robust efficacy data

Components of Target Trial Protocol		Target Trial Specification (Hypothetical RCT)	Target Trial Emulation (Data from Transplant Centers)	AI/ML Used in this Study	Potential Use of AI/ML
1	Eligibility	cGVHD, age ≥ 12 years, received 2–5 prior LOTs	Eligibility specified in data collection and analytic dataset development		Data Curation
2	Treatment Strategies	Investigational agent vs. BAT with clearly defined LOT rules (what exactly is 1st, 2nd, 3rd, … lines)	LOTs algorithmically defined based on expert consultations and definitions adopted in RCTs		LOT Rules
3	Assignment Procedures	Randomized, open label	Definition of treatment assignment based on information at or before time zero		
4	Follow-up	Time zero = LOT initiation. Endpoint assessment at week-26.	Time zero = LOT initiation. Endpoint assessment at week-26 based on all information from time 0 to week-26.		
5	Endpoints	Dichotomous response indicating success/failure at week-26	Failure = death, relapse, LOT interrelation, or physician assessed non-response. Else Success.		Endpoint operational-ization
6	Causal Contrasts	Difference in population-level overall response (ORR) between investigational agent and BAT	Causally interpretable estimate for the difference in ORR between the two strategies	TMLE/ G-methods	
7	Identifying Assumptions	Randomization (met in an RCT)	Consistency, positivity, conditional exchangeability		
8	Analysis Plan	Difference in ORR along with 95% confidence intervals	TMLE, G-computation, with supportive and sensitivity analyses	TMLE/ G-methods	

BAT, best available therapy; cGVHD, chronic graft versus host disease; KM, Kaplan-Meier; LOT, line of therapy; ML, machine learning; ORR, overall response rate; TMLE, targeted maximum likelihood learning

Concluding remarks

AI offers promise in advancing RWE, supporting informed healthcare decisions and personalized care. AI/ML techniques can help strengthen clinical dossiers by leveraging:

- **Large Language Models** (LLMs) - To unlock critical insights from complex health care data with the potential to better leverage target trial framework and more closely emulate target trial

- **AI/ML driven analytical methods** – helping reduce bias, improve handling of missing data and enhance regulatory confidence in causal inference

IMPORTANT NOTICES:

- ***Forward-Looking Statements:*** This presentation may contain forward-looking information about AI methodologies in clinical research. Actual regulatory acceptance and implementation may differ materially from expectations.

- ***Intellectual Property:*** The methodologies discussed may be subject to intellectual property rights. This presentation does not grant any license or right to use such methodologies.

- ***Regulatory Compliance:*** All AI/ML applications in regulatory submissions must comply with applicable guidelines and requirements of relevant health authorities.

- ***Data Privacy:*** Any implementation of these methodologies must comply with applicable data protection and privacy laws.

- ***Professional Representation:*** The speaker represents the EUCOPE group in this forum while maintaining employment with Sanofi.