Research Proposal: Machine Learning Approaches to Assess Long-term Inclisiran Safety

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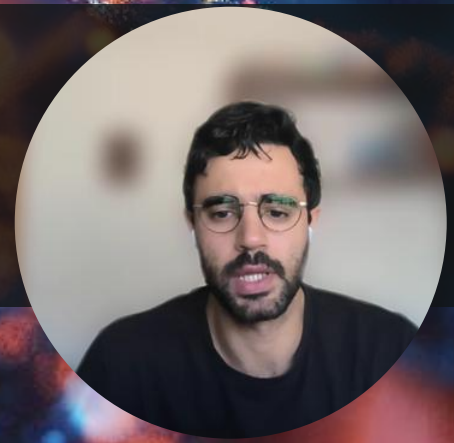
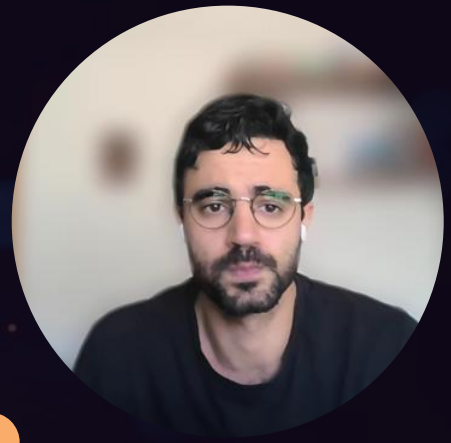
PgDip in Artificial Intelligence





Significance of the research

Adverse drug events (ADEs) remain a leading cause of harm in healthcare[1]

Cardiovascular disease (CVD) causes 17.9 million deaths globally each year[2]

Inclisiran: small interfering RNA (siRNA) drug that silences PCSK9 messenger RNA (mRNA), lowering LDL cholesterol by 44–54%, with only twice-yearly dosing[3,4]

Clinical trials show **generally safe profile**, but **follow-up limited to ~6 years**[5]

ORION-4: international randomised controlled long-term trial, including 15,000 patients with established atherosclerotic CVD (ASCVD)[6]

1. Kim, RH. *et al.* (2022) 'Analyzing adverse drug reactions using statistical and machine learning methods: a systematic review', Medicine, 101(25), p. e29387. Available at: doi.org/10.1097/MD.0000000000029387.
2. World Health Organization (2023) *Cardiovascular diseases (CVDs) fact sheet*. Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Accessed: 2 October 2025).
3. Marrs, J.C. and Anderson, S.L. (2024) 'Inclisiran for the treatment of hypercholesterolaemia', *Drugs in Context*, 13, p. 2023-12-3. Available at: doi.org/10.7573/dic.2023-12-3.
4. Ray, K.K., Wright, R.S., Kallend, D., *et al.* (2020) 'Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol', *New England Journal of Medicine*, 382(16), pp. 1507–1519. Available at: doi.org/10.1056/NEJMoa1912387.
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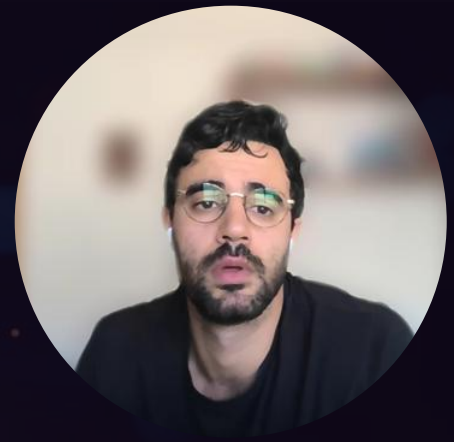


Research question

Can **Machine Learning (ML)** uncover **long-term inclisiran safety signals** beyond standard analyses?

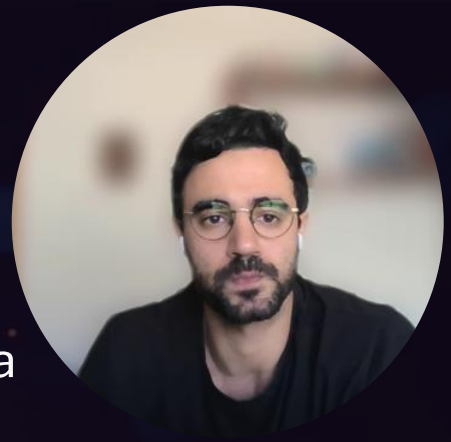
Data harmonisation (structured + unstructured)

Which ML models?

Added value from free-text?[7,8]

7. Hu, X., Zhang, Y., Li, J., *et al.* (2023) 'Leveraging natural language processing and machine learning to identify adverse drug events in clinical text', *Drug Safety*, 46(9), pp. 815–829. Available at: doi.org/10.1007/s40264-024-01505-6.
8. Murphy, R.M. *et al.* (2023) 'Adverse drug event detection using natural language processing: A scoping review of supervised learning methods', PloS One, 18(1), p. e0279842. Available at: doi.org/10.1371/journal.pone.0279842.

Aims and Objectives



Apply ML to ORION-4 data for **safety signal detection**

- Preprocessing data
- Develop ML models (supervised/unsupervised)[1]
- Benchmark against Cox regression & disproportionality methods[4]
- Validate signals with linked national datasets

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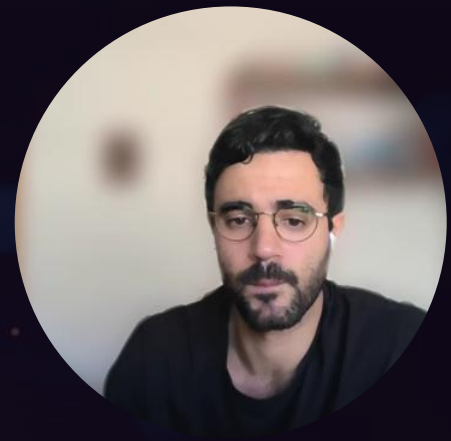
4. Ray, K.K., Wright, R.S., Kallend, D., *et al.* (2020) 'Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol', New England Journal of Medicine, 382(16), pp. 1507–1519. Available at: doi.org/10.1056/NEJMoa1912387.



Literature Review

Clinical Trials

- Statins first-line;
  PCSK9 monoclonal antibodies (mAbs) adjunct in high-risk groups[9,10]
- Inclisiran approved by EMA 2020, FDA 2021[3]
- ORION-9/10/11 trials:
  ~50% LDL-C reduction, safe, injection-site AEs[4]
- ORION-3/8 trials: long-term safety confirmed[5]

Machine Learning

- ML in pharmacovigilance: structured ADE prediction[1,8]
- NLP for free-text event extraction[7,8]

1. Kim, RH. *et al.* (2022) 'Analyzing adverse drug reactions using statistical and machine learning methods: a systematic review', Medicine, 101(25), p. e29387. Available at: 10.1097/MD.0000000000029387.
3. Marrs, J.C. and Anderson, S.L. (2024) 'Inclisiran for the treatment of hypercholesterolaemia', *Drugs in Context*, 13, p. 2023-12-3. doi:10.7573/dic.2023-12-3.
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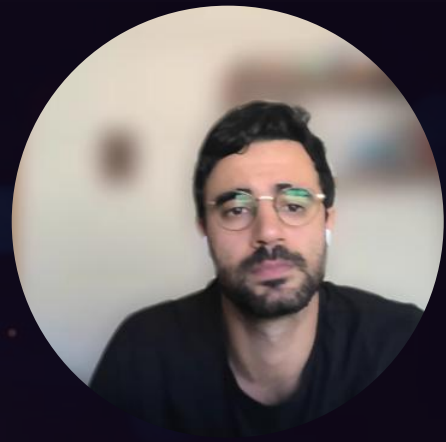
9. Grundy, S.M., Stone, N.J., Bailey, A.L., *et al.* (2019) '2018 AHA/ACC guideline on the management of blood cholesterol', *Journal of the American College of Cardiology*, 73(24), pp. e285–e350. Available at: doi.org/10.1016/j.jacc.2018.11.003.
10. Mach, F., Baigent, C., Catapano, A.L., *et al.* (2020) '2019 ESC/EAS Guidelines for the management of dyslipidaemias', *European Heart Journal*, 41(1), pp. 111–188. Available at: doi.org/0.1093/eurheartj/ehz455.

Methodology Overview



Data sources → **Preprocessing** → **ML models** → **Outputs**

Structured data: demographics, prescriptions, hospitalisations, Serious Adverse Event (SAE) reports

Unstructured data: free-text notes analysed with NLP[7,11]

Supervised classifiers (random forests, gradient boosting, neural networks)[8]

Unsupervised clustering[8]

NLP (transformer models)[8,11]

7. Hu, X., Zhang, Y., Li, J., *et al.* (2023) 'Leveraging natural language processing and machine learning to identify adverse drug events in clinical text', *Drug Safety*, 46(9), pp. 815–829. Available at: doi.org/:10.1007/s40264-024-01505-6.
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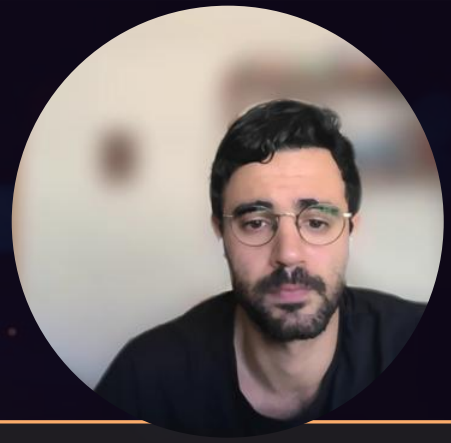
11. Li, Y. *et al.* (2024) 'Artificial intelligence-powered pharmacovigilance: A review of machine and deep learning in clinical text-based adverse drug event detection for benchmark datasets', Journal of Biomedical Informatics, 152, p. 104621. Available at: doi.org/10.1016/j.jbi.2024.104621.

Research Design



Harmonisation + feature engineering across datasets

Cross-validation with held-out test sets

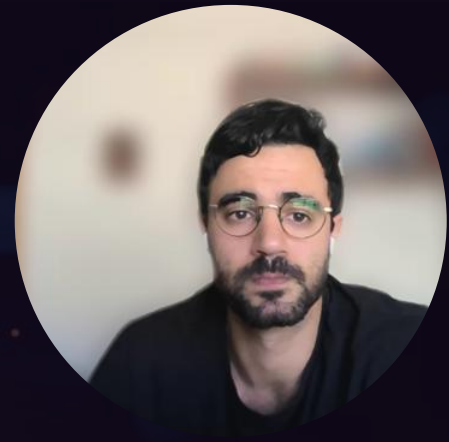
Benchmarks: Cox regression, disproportionality[4]

Performance metrics: AUROC, precision-recall, calibration

Explainability with SHAP to interpret outputs[12]

4. Ray, K.K., Wright, R.S., Kallend, D., *et al.* (2020) 'Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol', New England Journal of Medicine, 382(16), pp. 1507–1519. Available at: doi.org/10.1056/NEJMoa1912387.
12. Sadeghi, Z. *et al.* (2024) 'A review of Explainable Artificial Intelligence in healthcare', Computers and Electrical Engineering, 118, p. 109370. Available at: doi.org/10.1016/j.compeleceng.2024.109370.

Ethical Considerations & Risks



RISKS

Privacy

Subgroup bias

Spurious signals[13]

MITIGATIONS

GDPR pseudonymisation

Secure storage

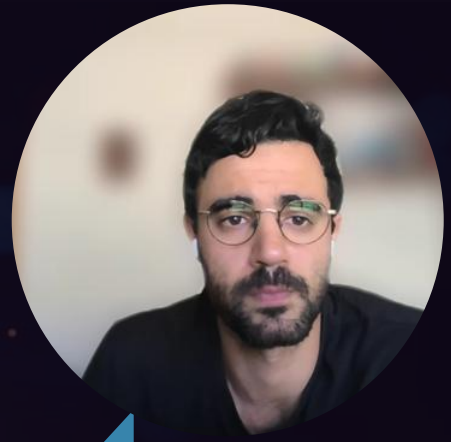
Fairness audits

Expert review

Ethical approvals

13. Rajkomar, A., Hardt, M., Howell, M.D., Corrado, G. and Chin, M.H. (2019) 'Ensuring fairness in machine learning to advance health equity', *Annals of Internal Medicine*, 169(12), pp. 866–872. Available at: doi.org/10.7326/M18-1990.

Timeline

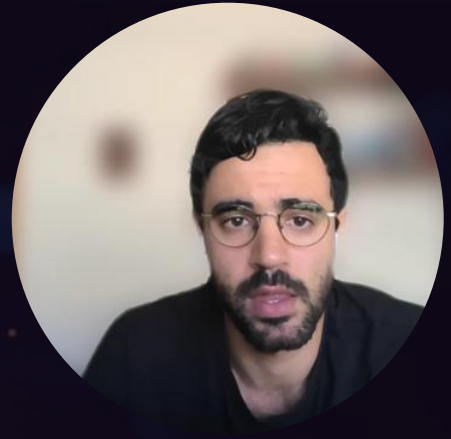


Review	Preprocessing	Modelling	Validation	Write-up
Literature review & ethics approval	Data preprocessing & NLP pipeline	Model development & internal validation	Benchmark comparison & external validation	Write-up & dissemination

MONTHS

1 4 7 10 13

Expected Contribution



First ML application to inclisiran safety[3,5]

Anticipates ORION-4 final results in 2026[6]

Framework for multimodal ADE detection

Transferable to other RNAi therapies[14]

3. Marrs, J.C. and Anderson, S.L. (2024) 'Inclisiran for the treatment of hypercholesterolaemia', *Drugs in Context*, 13, p. 2023-12-3. Available at: doi.org/10.7573/dic.2023-12-3.
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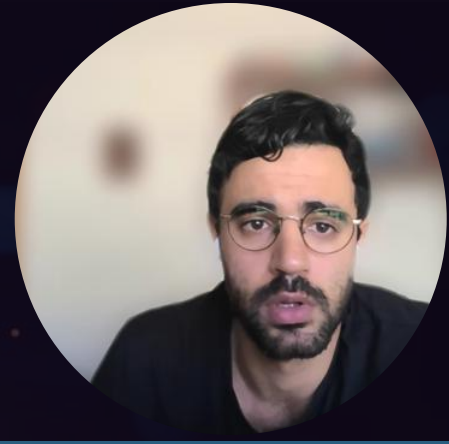
14. Fazoli, R.T., Drager, L.F., Kalil-Filho, R. and Generoso, G. (2024) 'RNA interference therapy in cardiology: will new targets improve therapeutic goals?', *Drugs in Context*, 13, p. 2024-3-1. Available at: doi.org/10.7573/dic.2024-3-1.

Conclusion



ML may provide earlier and deeper insights into long-term inclisiran safety

Inclisiran:
effective siRNA,
promising safety signals[3,4]

Scientific gap:
long-term safety unknown[5]

ORION-4:
unique dataset + robust causal framework[6]

ML may help detect
hidden safety pattern[1]

1. Kim, RH. *et al.* (2022) 'Analyzing adverse drug reactions using statistical and machine learning methods: a systematic review', Medicine, 101(25), p. e29387. Available at: doi.org/10.1097/MD.0000000000029387.
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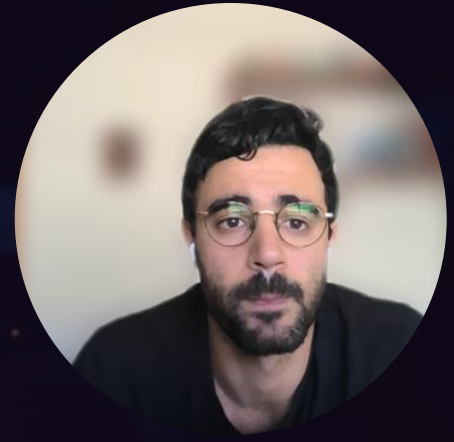

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Thank you