MRC-GAN: Extendibility and impact report

Abstract This report describes future work and a roadmap for the new virtual trial emulation approach that has been studied in the 6-month MRC-GAN research project. Our research in this report has been focused on potential exploitation of the technologies in support of clinical research in multimorbidity. Randomised Controlled Trials (RCTs) have significant limitations in external validity. Especially, many RCTs only select patients with single diseases, excluding those with perceived vulnerabilities. There is a major concern over the scarcity of available information about many clinical conditions that cannot be provided by RCTs. Consequently, a key drawback of the current clinical guidelines is that most of them only address single diseases with very few recommendations for multimorbidity. Answers to many key clinical questions about people with multimorbidity and other perceived vulnerabilities can be found in real-world data. However, contributions of the existing observational studies with real-world data are hindered by many key barriers including their inherent observational nature. In contrast, the virtual trial emulations are interventional and hence support counterfactual emulations to gain quantitative insights into the treatment effects of hypothetical interventions on multimorbidity. This offers a time/cost saving, and privacy-preserving solution to extrapolate RCT outcomes to tailored populations and represents a new way to provide real-world evidence to support future clinical research. Our research is among the first to combine generative AI and causality learning to support full trial emulation with causal inference. The report has recommended that in future work we need to focus on quality calibration of the trial emulations; carry out further clinical evaluations through a wider set clinical use cases; build strong network with stakeholders such as clinical guideline developers and regulators; and support benefit assessment in a wider context including the involvement of health economic models.

The report is organised as follows: Section 1 gives an overview of the project outcomes. Section 2 presents the limitation of the existing clinical guidelines and trials in providing information about treating people with vulnerabilities, especially those with multimorbidity. Section 3 describes future scenarios in which the trial emulations can be used to extrapolate RCT outcomes in clinical practice, with their potential impact on multimorbidity and scientific advance. Section 4 provides future steps to further advance the research and clinical adaptation of the trial emulations.

1. Overview of project outcomes

Project context and method The MRC-GAN research project is designed to investigate an alternative approach to support clinical research through the use of synthetic data. We study the feasibility of running virtual clinical trial emulations to extrapolate randomised clinical trials to cover real-world populations. The emulations generate synthetic populations that preserve the same value for research as real patient data under the support of the latest generative AI and causality learning technology. We have studied the feasibility of this new approach through a specific use case in the context of Type 2 diabetes mellites (T2DM). We have assessed the results by comparing the outcomes from the trial emulation with the real clinical trial results (i.e. LEAD-5: Liraglutide Effect and Action in Diabetes[35]). SCI Diabetes in the Safe Haven platform [33] provides a good dataset in this study. This is an inclusive national dataset of individuals with diabetes containing a broad range of longitudinal demographic, phenotypic, biochemical and screening data. There are approximately 300K individuals with diabetes. Over 3K individuals with MODY (Maturity-onset diabetes of the young) are recorded with certainty (genetic information) along with records of individuals with negative genetic test results.

Project outcomes and conclusions The primary research questions include:

- Can we generate synthetic data that preserve the same value for research as real-world health data?
- Can we perform virtual clinical trial emulations by discovering correct causal relations from the synthetic data?

The first question is answered with measurable evidence gained through experiments to (**a**) learn a causality model from the real-world health data on the Safe Haven platform. The causality model is integrated into a generative process to generate synthetic data that preserve the same data distributions as the real data. The distance between the real and synthetic data distributions are measured with specific metrics[34, 38]; (**b**) make statistical comparisons between real and synthetic data; (**c**) compare regression analysis and feature importance ranking within the real data versus synthetic data.

The second question is answered with measurable evidence in (**a**) comparisons of the effect size of three drugs (i.e. *GLP-1*, *basal insulin* and *placebo*) calculated from the virtual trial emulations against those acquired from LEAD-5. According to the emulations, *GLP-1* reduces HbA_{1c} significantly vs *placebo* and *basal insulin*, and hence has the best performance measured by HbA_{1c} and BMI reduction compared with the other two drugs in the patient population that meet the inclusion criteria of LEAD-5. This is largely in agreement with the results from LEAD-5; (**b**) extended counterfactual emulations to predict the effect sizes on real patient data. Experiments with real patients who do not fall into the baseline characteristics of LEAD-5 have presented different performance rankings between the drugs, suggesting that the LEAD-5 trial outcomes cannot be simply extrapolated to cover other patient populations. To this end, the virtual trial emulation models and tools are potentially very useful in terms of providing evidence to support the extrapolation of clinical trials for real-world clinical practice.

2. Limitations of clinical trials and guidelines

Randomised Controlled Trials (RCTs) have long been considered as the 'gold standard' to inform clinical guidelines[1]. However, they have significant limitations in external validity. The trial outcomes and conclusions are only directly applicable to the subjects involved in the studies, who might not be representative to the entire real-world population. Especially, many RCTs only select patients with single diseases, excluding those with perceived vulnerabilities such as older individuals, adolescents, individuals with concomitant conditions, multimorbidity, concomitant medication use, and polypharmacy[2-9]. This is due to several restrictions in conducting RCTs: Many RCTs have overly stringent exclusion criteria to exclude patients with vulnerabilities; conducting RCTs for rare conditions is practically very difficult; it is not feasible to carry out a trial for every disease combination across demographics to cover all types of multimorbidity; there are ethical restrictions to subjects such as adolescent individuals, and so on and so forth. Hence, many individuals with vulnerable characteristics in the real-world are not well represented in the RCT outcomes. Consequently, this leaves a significant knowledge gap with no answers to many important clinical questions.

Clinical guidelines have been developed based on the evidence provided from clinical trials. There is a major concern over the scarcity of available information about many clinical conditions that cannot be provided by RCTs. The complexity of patients with multimorbidity and polypharmacy renders many of the existing clinical guidelines both in the UK[15] and worldwide[16] inadequate [17]. There are increasing questions whether these guidelines provide adequate support to clinical decision making for heterogeneity of diseases. A key drawback of the current clinical guidelines is that most of them only address single diseases with very few recommendations for multimorbidity [10] to inform doctors and patients about the "net" treatment benefits and risks. Multimorbidity is rarely accounted for in treatment recommendations. This issue has been identified by numerous studies. For example, a recent analysis [18] on three conditions in Type 2 diabetes mellites (T2DM), heart failure and depression have found that the trials underpinning treatment recommendations in the associated guidelines largely excluded older patients and people with multimorbidity. Further examinations of the drugs that were recommended for the treatment of these three conditions found that 27 out of 32 potentially serious drug–disease interactions were for comorbid chronic kidney disease. They have also identified common cases of potential serious drug-drug interactions between the drugs recommended for these three conditions in the clinical guidelines (133 for type 2 diabetes, 89 for depression, 111 for heart failure). Indeed, applications of individual disease guidelines to manage multimorbidity can be potentially harmful [19] with unrecognized treatment burden [20,21]. According to some research[22], clinicians struggle to balance the benefits and risks of multiple recommended treatments for people with multimorbidity. A qualitative research [23] stated that 'inadequacy of guidelines and evidence-based medicine' was identified as a common issue particularly in relation to the extrapolation of evidence from RCTs to multimorbidity. Correspondingly, clinical practices for people with multimorbidity often involve considerable deviations from the clinical guidelines [23,24]. Studies have also discovered that there is a significant difference between the subjects involved in clinical trials and the real-world population that have received the treatments in clinical practice. According to [18], approximately 40% of people newly diagnosed with T2DM in Scotland in 2008 would have been excluded for RCTs based on age alone, and these excluded older people had much higher levels of multimorbidity.

3. Benefit and potentials of virtual trial emulations

3.1 Future benefits from using virtual trial emulations

Answers to many key clinical questions about people with multimorbidity and other perceived vulnerabilities can be found in real-world data that are routinely and continuously collected over a long period of time in clinical practices, which entail a broad picture of heterogenous population in the real world. Typically observational studies are involved to study the real world data. However, contributions of the existing observational studies are hindered by many key barriers: routinely collected data are typically imbalanced across population, diseases and interventions; noise and missing measurements are present; lengthy time and significant effort are needed to remove patient identifiable information. More importantly, observational studies have inherent limitations in their ability to identify treatment effects due to their observational nature, as treatment choices and outcomes may depend on unknown confounders, which can invalidate the studies. So far most of the existing observational studies have only targeted very limited clinical questions and their potential remains untapped for clinical research[13,14].

Our research targets causation driven virtual trial emulation, which is an innovative evidence-based approach to address the abovementioned challenges in observational studies by allowing us to leverage real-world data to extrapolate RCT outcomes tailored to targeted populations and seek answers to key clinical questions that cannot be provided by RCT studies, including those concerning patients with vulnerabilities. In contrast to conventional observational studies which have an inherent observational nature, the virtual trial emulations under our experiments are *interventiona*l and hence support *counterfactual* emulations and calculations. They are based on causality learning to capture causal relations between multiple data variables. The trial emulations compare differences of the variables that measure treatment effects between a treatment and a control group, both of which consist of virtual synthetic populations. The synthetic cohorts are generated to meet the specific inclusion criteria that are defined by clinical experts to answer target clinical questions. Noticeably, in our trail emulation approach, causal relations and structures learned from real-world observational data are inherently incorporated into the generative AI model for the synthetic data generation. This renders synthetic cohorts, in which all of the variables are statistically distributed according to their underlying causal relations. The differences lying within the synthetic cohorts between the treatment and control groups allow the clinical experts to gain quantitative insights of the treatment effect, predict potential outcomes for hypothetical interventions and enable comparisons between different treatments.

While the experiments that have been carried out so far in the MRC-GAN project are focused on the T2DM use case with a single target drug, the AI technology behind the virtual trial emulations is generic and can potentially be applicable to a very wide range of treatments for different health conditions in the context of extrapolating RCT outcomes to cover larger populations, especially for those with vulnerabilities. Health professionals will be able to run emulations on their target population, examine the outcomes of the emulations and make a judgement on whether the effect sizes calculated from the emulations provide right answers about their clinical questions. Specifically, we envisage the following future usage of the trial emulations that is not tied to any specific clinical conditions.

- Health professionals view the quality of the synthetic data and the similarity of the synthetic patients to their target population by using data quality indicators to assess the “fidelity” of the synthetic population, especially to examine how the causality-associated data characteristics are preserved in the synthetic data.
- Information about potential bias and uncertainty from the emulations is also made available to allow the health professionals to understand the extent (where, when and how much) that the emulation outcomes are applicable, and to make them aware of the deviation of the effect size in the presence of the uncertainties.
- Health professionals can be informed about the quality of the trial emulation models and the reliability of the trial emulations by using standardised benchmarking and performance indicators, which offer tangible evidence to support clinical decision making based on the trial emulation results.

The virtual trial emulation tools together with their performance metrics will bring valuable evidence with increased transparency to clinical research and to future clinical decision making. This will contribute to the trustworthiness of the virtual trial emulation based approach and facilitate its future clinical adaptation and acceptance. Overall, the causation driven virtual trial emulations offer a time /cost saving, and privacy-preserving solution to extrapolate RCT outcomes to tailored populations by representing a new way to provide real-world

evidence to support future clinical research. The emulations can be tailored to create virtual populations to address target clinical questions via trial emulations, which would otherwise be impossible to address in real-world RCTs. The emulated trials offer high quality synthetic data that preserve the same value for research as the real datal to deliver reliable evidence and insights in treatment efficacy. Compared with anonymised real data (which contains reduced information about real patients), synthetic data can address their main caveats including bias, data imbalance, noise and missing measurements. They are also in a much better position to overcome legal barriers in data protection and sharing. This will open doors for further research in this direction, which could ultimately bring a landscape change to revolutionise future biomedical and health research by broadening its research agenda, liberating its restrictions, saving cost and time. Research in this direction will speed up new timelines for treatment discovery, address increasingly complex healthcare landscape in elderly population and multi-morbidity, and potentially transform regulatory and policy making process.

3.2 Potential impact on multimorbidity

While the virtual trial emulations are designed to accelerate new knowledge discovery in a wide variety of clinical domains where RCTs face challenges, multimorbidity is properly one of the most relevant areas to which the trial emulations can make direct contributions. Multimorbidity is the presence of multiple long-term conditions on individual patients. Multimorbidity is associated with higher mortality, lower quality of life, increased difficulties in care co-ordination and heavier treatment burden[25-32]. People with multimorbidity have the highest health needs and are the highest users of health care. Majority of people aged over 65 and majority of patients with chronic conditions have multimorbidity. Multimorbidity is becoming the norm, as a sharp increase of overall multimorbidity cases across the population has been observed[11,12]. The majority of people who are the target of most adult single-disease guidelines will have comorbidity [18]. The existing problems and limitations in RCTs and clinical guidelines present a significant challenge in healthcare as the increase of multimorbidity across the population is becoming clearly evident[11,12]. Ensuring appropriate treatment for them is therefore a priority.

3.3 Scientific advance

The virtual trial emulations move beyond the conventional observational study approaches [13,14] by overcoming their inherent observation nature to enable interventional experiments to test and compare hypothetical and counterfactual treatment effects. Our research is among the first to combine generative AI and causality learning to support full trial emulation with causal inference. Synthetic patient populations can be generated according to different inclusion criteria of the trials that are designed to explore different clinical questions for targeted populations. This research work also contributes to delivering new knowledge about using synthetic data to complement the use of real world health data and RCTs. Computer simulations have started to demonstrate potential in clinical trials [35] and there is increasing attention on using synthetic data to create the control arms [37] (where no causal inference is needed). Our work advances the state-of-the-art in research by leveraging on the advance in causality learning and generative AI to support full trial emulations involving both the control and treatment arms. This opens new avenues for using synthetic data in support of health research.

4. Future steps

We have identified the following areas of future work for the causation-driven virtual trial emulations:

- Trial quality calibration

To move forward, we need to seek answers to further key questions regarding reliability, safety and trustworthiness of the trial emulation approach by investigating its quality calibration metrics. We need to deliver a set of quality indicators and benchmarks for the synthetic data alongside the methods that are designed to evaluate the trial emulation quality with these indicators. Health professionals will need to use these evidence to judge whether the emulation provides right answers to the clinical questions about their patients. Further, to support real-world clinical decisions, the quality calibration will also need to indicate when they are likely be inaccurate. To this end, the quality metrics will include potential bias estimation in the presence of uncertainties, such as unobserved confounders and non-identifiable causal relations in the data. The metrics should relax the assumptions made during the causality learning process on the non-existence of hidden confounding and non-identifiable causal relations to indicate the potential deviations from the trial emulations if these assumptions are not held. We will also need to take into account other aspects in robustness, reproducibility and transparency. It will contribute to its trustworthiness and build foundations for future quality control and certification of the trial emulation approach.

- Further clinical evaluations

The concept needs to be evaluated through a wider set of clinical cases. Exemplar conditions may involve T2DM, heart failure and chronic obstructive pulmonary disease (COPD), as these conditions are associated with large population and they are commonly comorbid with each other. Existing literatures have identified significant knowledge gaps in treating and managing multimorbidity in these clinical areas [18]. Also, there is a good number of established clinical trials in these clinical areas, allowing further confirmative studies to replicate these trials (as we did in this pilot study) in future work. The retrospective health datasets that are available on the Safe Haven platform in NHS Greater Glasgow and Clyde[33] are very general and useful in the future research, as they contain health records over 1 million population in Glasgow and beyond. The retrospective data can be used not only to train the emulation models, but also to check against the trial population to identify its difference from the real-world treatment population.

Other interesting areas to apply trial emulations may include cancer research. We can design specific use cases such as lung cancer clinical decision support, in which we can experiment with the use of trial emulations for lung cancer risk assessment from clinical, demographics and image data. Potential risk factors include age, smoking status, medical history and so on. Human decisions based on the trial emulations will enable the identification of patients with high risks at early stage for timely interventions. Image data will contribute to the risk calculation. Synthetic images will be generated to display the hypothetical outcomes under alternative actions. We can use an established large-scale retrospective dataset, which is the National Lung Screen Trial (NLST) database [9] from the first US- led study to demonstrate the benefit of lung cancer screening with low-dose CT (LDCT) for reducing mortality rates. Data acquired from this trial consist of approximately 75,000 LDCT studies acquired at yearly intervals (including patients with biopsy proven tumours, and healthy controls).

- Working with clinical guideline developers and regulators

In addition to further technical explorations, we need to build a sustainable network community with a wide range of potential stakeholders, including clinical guideline developers, regulators, health professionals, health economists, policy makers and pharmaceutical industry. Clinical guideline developers are among the most direct and relevant stakeholders to benefit from the outcomes of this research. Previous studies have identified the problems in the existing clinical guidelines, both in the UK[15] and in other countries such as US[16]. We can carry out new literature and clinical guideline reviews to update the findings from the previous studies. This will allow us to identify to what extent the knowledge gap exists in the existing clinical guidelines together with the RCTs that have informed these clinical guidelines. The outcome of the reviews will help us design virtual trials for further validation of the trial emulations in the context of extrapolating the RCT outcomes.

We will need to exchange ideas with the stakeholders to build a common understanding of the trial emulation, and a shared vision on theπ adaption in the future clinical guideline development. We will need to build further network and community activities to enhance communications. It will also be beneficial to run experiments involving clinical and other relevant experts, who will be presented with multimorbidity evidence from the trial emulation to see if this can help improve the clinical guidelines.

- Benefit assessments in a wider context

Future work should also move beyond taking only clinical measurements (e.g. blood pressure, clinical tests) for treatment benefit assessment by supporting benefit estimation in a wider context, including the use of health economic figures and the assessment of efficiency in health service provision. This may include a wider range of real-world datasets to examine time to benefit [18].

5. References

1. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine – new approaches and challenges. *Acta Inform Med* 2008; **16:**219–25.
2. Buffel du Vaure C, Dechartres A, Battin C, Ravaud P, Boutron I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. *BMJ Open 2016*; 6: e012265.

3. Stoll CRT, Izadi S, Fowler S, et al. Multimorbidity in randomized controlled trials of behavioral interventions: a systematic review. *Health Psychol* 2019; 38: 831–39.
4. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; 23: 3112–24.
5. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med* 2011; 26: 783–90.
6. Kronish IM, Fenn K, Cohen L, et al. Extent of exclusions for chronic conditions in breast cancer trials. *JNCI Cancer Spectr* 2018;2: pky059.
7. Martin RC, DiBlasio CA, Fowler ME, Zhang Y, Kennedy RE. Assessment of the generalizability of clinical trials of delirium interventions. *JAMA Netw Open* 2020; 3: e2015080.
8. Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007; 297: 1233–40.
9. He J, Morales DR, Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. *Trials* 2020; 21: 228.
10. Lugtenberg, M., Burgers, JS., Clancy, C., Westert, GP., Schneider, EC. (2011) Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. *PLoS One* 6: e25987.
11. Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. *BMC Public Health* 2015;15: 415.
12. Cassell A, Edwards D, Harshfield A, et al. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2018; 68: e245–51.
13. L. G. Hemkens et. al, Routinely collected data and comparative effectiveness evidence: promises and limitations, *CMAJ,* May 17, 2016,
14. Mc Cord et. al. Routinely collected data for randomized trials: promises, barriers, and implications, *Trials* (2018) 19:29
15. Hughes L, Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age & Ageing* 2013.
16. Sinnott C, et al. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. *BMJ Open* 2013;3:e003610.
17. Muth, C. et al Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. *J Intern Med* 2019;285:
18. Guthrie B, et al. Better guidelines for better care: accounting for multimorbidity in clinical guidelines – structured examination of exemplar guidelines and health economic modelling. *Health Serv Deliv Res*2017 ;5(16).
19. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for perfor- mance. *JAMA* 2005; 294: 716–24.
20. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ* 2009; 339: b2803.
21. Montori VM, Brito J, Murad M. The optimal practice of evidence-based medicine: Incorporating patient preferences in practice guidelines. *JAMA* 2013; 310: 2503–4.
22. O'Brien R, et al. An 'endless struggle': a qualitative study of general practitioners' and practice nurses' experiences of managing multimorbidity in socio-economically deprived areas of Scotland. *Chronic Illn* 2011; 7:45–59.
23. Sinnott C, et al. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. *BMJ Open* 2013;3:e003610.
24. Sinnott C, Hugh SM, Boyce MB, Bradley CP. What to give the patient who has everything? A qualitative study of prescribing for multimorbidity in primary care. *Br J Gen Pract* 2015;65:e184–91.
25. Barnett K, et al. Epidemiology of multimorbidity and implications for health care, research, medical education: a cross-sectional study. *Lancet* 2012
26. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu A, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004;2:51. http://dx.doi.org/ 10.1186/1477-7525-2-51

27. Fortin M, Hudon C, Dubois M, Almirall J, Lapointe F, Soubhi H. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. *Health Qual Life Outcomes* 2005;3:74. http://dx.doi.org/10.1186/1477-7525-3-74
28. Gallacher K, Batty GD, McLean G, Mercer S, Guthrie B, Langhorne P. Stroke, comorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. *BMC Med* 2014;12:151. http://dx.doi.org/10.1186/ s12916-014-0151-0
29. Payne RA, Abel GA, Guthrie B, Mercer SW. The effect of physical multimorbidity, mental health conditions and socioeconomic deprivation on unplanned admissions to hospital: a retrospective cohort study. *CMAJ* 2013;185:E221–8. http://dx.doi.org/10.1503/cmaj.121349
30. Duerden M, Avery A, Payne R. Polypharmacy and Medicines Optimisation: Making It Safe and Sound. London: *The King's Fund*; 2013.
31. O'Brien R, Wyke S, Guthrie B, Watt G, Mercer SW. The 'everyday work' of living with multimorbidity in socioeconomically deprived areas of Scotland. *J Comorbidity* 2014;4:1–10. http://dx.doi.org/10.15256/joc.2014.4.32
32. Lawson K, Mercer S, Wyke S, Grieve E, Guthrie B, Watt G. Double trouble: the impact of multimorbidity and deprivation on preference-weighted health related quality of life a cross sectional analysis of the Scottish Health Survey. *Int J Equity Health* 2013;12:67. http://dx.doi.org/ 10.1186/1475-9276-12-67
33. NHS Greater Glasgow and Clyde & NHS Tayside Health Board area data https://www.nhsggc.scot/staff-recruitment/staff-resources/research-and-innovation/nhsggc-safe-haven/
34. Petkov, H. Hanley, C., Dong, F., Causality Learning with Wasserstein Generative Adversarial Networks, International *Journal of Artificial Intelligence and Applications (IJAIA*),13(3), 2022
35. Russell-Jones, D., Vaag, A., Schmitz, O., Sethi, B K, Lalic, N, Antic, S., Zdravkovic, M., Ravn, G M, Simó, R; Rigato,M.,Fadini,G.P.(2014), Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial, *Randomized Controlled Trial, Diabetologia* 2009 Oct;52(10):2046-55.
36. Ionescu, C. M. et al, An Open Source Patient Simulator for Design and Evaluation of Computer Based Multiple Drug Dosing Control for Anesthetic and Hemodynamic Variables, *IEEE Access*, 2021
37. https://www.gov.uk/government/news/mhra-to-receive-nearly-1m-beis-funding-to-unlock-digital-data-and-scientific-regulatory-innovation
38. Arthur Gretton, Karsten M Borgwardt, Malte J Rasch, Bernhard Schölkopf, and Alexander Smola. A kernel two-sample test. *Journal of Machine Learning Research*, 13(Mar):723–773, 2012.