Institution: University of Nottingham		
Unit of Assessment: 10		
Title of case study: Informing international regulatory policy for drug safety using cardiac electrophysiology modelling		
Period when the underpinning research was undertaken: 2016 – 31 December 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Gary Mirams	Principal Research Fellow Professor of Mathematical Physiology	Nov 2016 – July 2019 August 2019 – present
Period when the claimed impact occurred: 2017 – present		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

The United States Food and Drug Administration (FDA) reviews safety data for all new pharmaceutical compounds before approving them for use in the USA. Research by Professor Mirams at Nottingham informed new Comprehensive in-vitro Pro-arrhythmia Assay (CiPA) guidelines requiring the use of mathematical models of drug action on cardiac electrophysiology to predict the clinical risk of pro-arrhythmic side effects for every new drug. In 2019, the FDA adopted this CiPA approach as part of their cardiac safety assessment. The mathematical models, and importantly our associated work on uncertainty quantification for their predictions, are a fundamental component of the new approach to drug testing and approval.

Furthermore, international policy for drug safety testing is harmonised worldwide by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In a world-first development, ICH have re-opened a safety document (the ICH-S7B) to follow the FDA in using a mathematical modelling approach, now set to become regulatory policy for the pharmaceutical industry's drug development activity worldwide.

2. Underpinning research (indicative maximum 500 words)

All new pharmaceutical compounds must be carefully screened for unwanted side effects on the heart which can cause arrhythmias and sudden cardiac death – even non-cardiac drugs such as antihistamines and antipsychotics have been removed from the market because of cardiac side effects. It has been established that in the majority of these cases, block of cardiac ion channels by pharmaceutical compounds is responsible for the increased pro-arrhythmic risk. Several types of potassium, calcium and sodium ion channels are important in regulating cardiac electrophysiology and also prone to being blocked by pharmaceutical compounds.

Computational electrophysiology modelling uses Ordinary Differential Equation (ODE)-based models to describe ion channel activity, how ion currents govern membrane potential, and vice-versa, creating the intricate nonlinear feedback systems that control the electrical activity of the heart. Mirams develops and uses these models to predict the effects of drugs blocking multiple channels and the subsequent alterations to cellular electrophysiology and risk of pro-arrhythmia for humans. Simulated risk assessment is based on human mathematical electrophysiology models which capture many decades' worth of research about how ion currents interact to regulate whole-cell and whole-heart electrophysiology. Experimental data for a new potential drug compound takes the form of ion channel screening performed independently for a panel of cardiac ion channels that are overexpressed in non-cardiac cell lines. The biophysically-based mathematical models are then used to integrate the new compound's experimental data, and predict the overall effect of the compound on a heart cell, and whether it is likely to increase pro-

arrhythmic risk. Since moving to Nottingham in 2016, Mirams has worked on various projects to advance and disseminate the use of simulations in a pharmaceutical regulatory setting. He also has ongoing collaborations with other pharmaceutical industry partners on joint research projects.

Mirams' work on techniques for uncertainty quantification (characterising uncertainty in simulation inputs/parameters and propagating it through to simulation outputs) in the context of ion channel block and subsequent simulations of cardiac electrophysiology has been critical in influencing international policy. These techniques are crucial in allowing regulators to make informed decisions about the reliability of model predictions by attaching probabilities to simulation outcomes, in this case a human clinical pro-arrhythmic risk score for a drug compound.

In a 2017 Wellcome Open Research paper **[1, 6]**, Mirams developed a hierarchical Bayesian inference method, and provided open source code, to characterise uncertainty in 'IC50 values' (the concentrations at which drugs block ion channels by 50%) from multiple ion channel screening experiments, the primary input into simulations of drug action on ion channels in the heart.

In a joint research paper **[2, 6]** with the United States Food and Drug Administration (FDA) – the world's leading pharmaceutical regulator – Mirams used the concept from the previous paper **[1, 6]** to characterise uncertainty in dose-response screening results (simulation inputs) and extended this to a Markov Chain Monte-Carlo approach for parameterising a larger number of input parameters which characterise the kinetic binding of drugs to a particularly important potassium channel. Mirams provided regular guidance, ideas and supervisory input to the FDA researchers who implemented these simulations. The second half of their joint paper describes the implementation of an uncertainty propagation technique to perform uncertainty quantification for the proposed simulated risk marker.

Mirams then worked with the FDA to design and carry out a prospective study to validate the risk marker **[3, 6]**; his input was invaluable in enforcing a blinded validation set. Mirams then assisted with performing this evaluation and in running a second set of simulations independently with our own in-house code, to provide extra confidence that the FDA's code and results were bug-free. Mirams has also worked with the FDA on guidelines for standardising in-vitro ion channel screening experiments and dealing with variability in their results in the CiPA approach **[4, 7]**.

Since 2018 Mirams has worked with the FDA to reach an academic, industry and regulatory community consensus on general principles for future evaluation and deployment of improved simulation risk markers. He chaired a workshop of experts including FDA modellers at a Cardiac Safety Research Consortium meeting to discuss these principles. This meeting gave the first draft of a set of principles for model evaluation. Mirams then worked to refine and get a broad consensus on these principles from a large number of additional cardiac modelling groups, and is second author on an arising publication in Clinical Pharmacology & Therapeutics describing these principles **[5, 7]**.

3. References to the research

NB: University of Nottingham staff (at the time of publication) are shown in bold.

Underpinning references:

1. RH Johnstone, R Bardenet, DJ Gavaghan, **GR Mirams** (2017). *Hierarchical Bayesian inference for ion channel screening dose-response data.* Wellcome Open Research 1:6. https://doi.org/10.12688/wellcomeopenres.9945.2
2. KC Chang, S Dutta, **GR Mirams**, KA Beattie, J Sheng, PN Tran, M Wu, WW Wu, T Colatsky, DG Strauss, Z Li (2017). *Uncertainty quantification reveals the importance of data variability and experimental design considerations for in silico proarrhythmia risk assessment.* Frontiers in Physiology 8:917 https://doi.org/10.3389/fphys.2017.00917

3. Z Li, B Ridder, W Wu, J Sheng, P Tran, M Wu, A Randolph, RH Johnstone, **GR Mirams**, Y Kuryshev, J Kramer, C Wu, W Crumb, D Strauss (2018). *Assessment of an In Silico Mechanistic Model for Proarrhythmia Risk Prediction under the CiPA Initiative*. Clinical Pharmacology & Therapeutics. 105(2):466-475. https://doi.org/10.1002/cpt.1184
4. BJ Ridder, DJ Leishman, M Bridgman-Taylor, M Samieegohar, X Han, WW Wu, A Randolph, P Tran, J Sheng, T Danker, A Lindqvist, D Konrad, S Hebeisen, L Polonchuk, E Gissinger, M Renganathan, B Koci, H Wei, J Fan, P Levesque, J Kwagh, J Imredy, J Zhai, M Rogers, E Humphries, R Kirby, D Stoelzle-Feix, N Brinkwirth, MG Rotordarm, N Becker, S Friis, M Rapedius, T Goetze, T Strassmaier, G Okeyo, J Kramer, Y Kuryshev, C Wu, H Himmel, **GR Mirams**, DG Strauss, R Bardenet, Z Li (2020). *A Systematic Strategy for Estimating hERG Block Potency and Its Implications in A New Cardiac Safety Paradigm*. Toxicology and Applied Pharmacology 394:114961. https://doi.org/10.1016/j.taap.2020.114961
5. Z Li, **GR Mirams**, T Yoshinaga, B Ridder, X Han, J Chen, N Stockbridge, T Wisialowski, B Damiano, S Severi, P Morissette, P Kowey, M Holbrook, G Smith, R Rusmusson, M Liu, Z Song, Z Qu, D Leishman, J Steidl-Nichols, B Rodriguez, A Bueno-Orovio, X Zhou, E Passini, A Edwards, S Morotti, H Ni, E Grandi, C Clancy, J Vandenberg, A Hill, M Nakamura, T Singer, L Polonchuk, A Greiter-Wilke, K Wang, S Nave, A Fullerton, E Sobie, M Paci, FM Tshinanu, D Strauss (2020). *General Principles for the Validation of Proarrhythmia Risk Prediction Models: an Extension of the CiPA In Silico Strategy.* Clinical Pharmacology & Therapeutics 107(1):102-111. https://doi.org/10.1002/cpt.1647

Grant details and funding awards:

6. Wellcome Trust, Henry Dale Fellowship, Improving assessment of drug-induced cardiac risk with mathematical electrophysiology models (GBP534,961; 2014-2019; 101222/Z/13/Z; PI Mirams)
7. Wellcome Trust, Senior Research Fellowship in Basic Biomedical Science, Developing cardiac electrophysiology models for drug safety studies (GBP1,918,557; 2019-2024; 212203/Z/18/Z; PI Mirams)

4. Details of the impact (indicative maximum 750 words)

An existing regulatory framework decides whether a new drug candidate has (as a side effect) an unacceptable pro-arrhythmic risk. This framework relies on animal testing and then human clinical trials, which obviously cannot probe the required human outcome directly (as it is sudden cardiac death which is both rare and undesirable). Since 2005 studies have used a surrogate for proarrhythmic risk based on an electrocardiogram measurement (known as the 'QT interval') which is sensitive but not specific. Electrophysiology simulations open the possibility of more accurate risk prediction than existing regulatory approaches, and therefore increased safety of new drugs when they are brought to market.

Since 2013, the US Food & Drug Administration (FDA), the EU and UK drug regulators (EMA and MHRA), the Cardiac Safety Research Consortium, the Health and Environmental Sciences Initiative and the Safety Pharmacology Society have been leading an internationally-supported initiative to replace a human clinical pro-arrhythmic safety trial (the 'Thorough QT' study) with a combination of ion channel screening, mathematical electrophysiology modelling (as described in Section 2), human-derived cardiac muscle cell studies (either from induced pluripotent stem cells or unused donor hearts), and a more lightweight human electrocardiogram study. The proposal is known as CiPA – the Comprehensive in-vitro Pro-arrhythmia Assay (www.cipaproject.org).

CiPA was launched in 2013 and subsequently a great deal of work has gone into standardising ion channel screening and stem cell work. Alongside, Nottingham have been working with the FDA to establish and test the simulation approach.

Research in Nottingham has developed uncertainty characterisation techniques for the experimental data that feeds into CiPA simulations, and subsequent uncertainty quantification of simulation outputs **[1-5]**. Paper **[1]** drew the attention of regulators at the FDA to the role of uncertainty quantification and its approach was quickly adopted. The Director of Division of Applied Regulatory Science, FDA, reports:

> *"Prof. Mirams highlighted the importance of Uncertainty Quantification with his publication* **[1]** *which provided a method to characterize the uncertainty in dose-response curve parameters. We worked together with Prof. Mirams to design a full Uncertainty Quantification pipeline for propagating dose-response parameter uncertainty, and uncertainty in the kinetic action of drugs on the hERG channel, through to a new simulated risk marker in the publication* **[2]***. We then also worked together on a blinded validation exercise for the proposed CiPA Torsade Metric Score which we published in* **[3]***. These papers have critical impact on the CiPA Initiative and play an essential role in prompting the International Council for Harmonisation to initiate the process of revising the current international cardiac safety regulatory guidelines."* **[D]**

The subsequent joint publication with the FDA **[3]** led to changes in the proposed clinical risk marker outputted from the simulations. The new proposed risk marker was tested in the Nottingham-FDA validation study **[3]**, found to provide excellent predictions, and is now the FDA's primary pre-clinical risk marker to assess the pro-arrhythmic risk of all 'new molecular entities' (pharmaceutical drugs).

Since January 2017 Mirams has been a member of the CiPA Steering Committee and sits on the in-silico working group **[E]**. He presented evidence at an FDA public hearing on 'Model Informed Drug Discovery' in Washington DC on 5th March 2017, where a panel of external experts voted in favour of implementing the central proposals of CiPA **[B**, Mirams main contribution pages 53-62**]**. In November 2017, Mirams organised a meeting in Toronto attended by around 80 delegates in which the academic cardiac modelling community presented their work to the FDA, and vice-versa **[A, D]**.

The FDA adopted the mathematical modelling approach in 2019:

> "*As of 2019, FDA is accepting and reviewing new drug submissions that include ion channel data assessed by CiPA protocols being used as inputs to an integrated [simulated] risk assessment procedure; and FDA is encouraging sponsors to use the uncertainty quantification techniques, rigorous validation of risk markers and principles established in the joint papers with Prof. Mirams to validate each sponsor's own proarrhythmia risk prediction models*" **[D]**

Internationally, the requirement of regulators for safety assessment (that pharmaceutical companies are required to provide) are agreed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (the ICH, https://www.ich.org). The ICH guidelines are agreed by government regulators from the USA, Europe, Japan, Canada, Brazil, South Korea, China, Singapore, Turkey and Switzerland, and are followed by almost all other countries in the world. The ICH guidelines relevant for cardiac pro-arrhythmic risk safety testing for all new drugs are ICH-S7B for pre-clinical (i.e. before first-time-in-human) testing and ICH-E14 for clinical (i.e. human) studies.

In light of the performance of the simulated risk marker, in November 2018 the ICH agreed to re-open the relevant guidelines (ICH-S7B) for modification to include such simulations pre-clinically (and comparison with them clinically) as the standard way of assessing a new compound's pro-arrhythmic risk **[E]**. This is an unprecedented action, and one directly linked to the Nottingham research. It is the first time an ICH guideline has been reopened to include mathematical modelling and only the second ICH guideline to even include such approaches. The other ICH guideline to include them is ICH-M7 for mutagenic impurity testing, which, from the outset, was formulated around Quantitative Structure Activity Relationships, a regression technique widely used in drug development; ICH-S7B is thus the first guideline to be re-opened to include

mechanistic mathematical modelling, in this case to predict the effect of drugs on the electrophysiology of cardiac muscle cells via a computer simulation, using biophysical principles.

The ICH-S7B draft Q&As was open to public consultation between 28 August 2020 and 28 November 2020, and public comments will be incorporated in a June 2021 version as finalised Q&As, containing additional guidance to help interpret the ICH-S7B and ensure smooth implementation **[D, F]**. It is anticipated that the technical training material and publication on the ICH website will occur between July 2021 and January 2022. In January 2022, new timeline and/or recommendations for proceedings with stage 2 will follow **[G, slides D1S01-Strauss p.27]**. Once this modification is complete, all global pharmaceutical regulators will have agreed to use the simulation approach as part of their procedures underpinning submissions to FDA for approval on new drugs. In the meantime, the pharmaceutical industry is engaged with the discussions and keeping a close watch as it develops.

A member of the CiPA Steering Committee and ICH Implementation Working Group reports: "*As part of the [ICH] Implementation Working Group assessing revisions for this document, I can assure you that Professor Mirams' work is playing prominently in discussions on modifications to this guidance. When accepted these revisions will influence the evaluation of electrophysiological cardiac safety studies conducted by the pharmaceutical industry and scrutinized by regulatory authorities worldwide.*" **[E]**

Aside from the global impact on the sector afforded by the revised regulation, Mirams' 2018-2019 work on establishing future principles for testing simulation improvements **[5]** has also had immediate impact on the ICH process. The FDA report:

"*In 2018 Prof. Mirams chaired a focus group at the Cardiac Safety Research Consortium CiPA Update Meeting* **[C]** *where he invited a panel of academic cardiac modelers to discuss principles for future improvements of the CiPA in silico program, focusing on reproducibility and validation of any new simulated risk markers. The new principles were authored by 42 experts from academia, industry and regulators and have just been accepted for publication* **[5]***. These principles also form the basis of some of the new ICH guidelines…*" **[D]**

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Cardiac Physiome Society's 20th Workshop: Metabolism, Mechanics and excitation, 6-9 November 2017, University of Toronto & CiPA Program
[B] FDA public hearing on 'Model Informed Drug Discovery (Hearing Transcript), 15 May 2017
[C] Cardiac Safety Research Consortium (CSRC), Meeting Agenda, 21-22 May 2018
[D] Letter of support from the Director of Division of Applied Regulatory Science, FDA, dated 19 January 2021
[E] Letter of support from a CiPA Steering Committee Member, AbbVie dated 19 October 2019
[F] ICH E14/S7B Q&A Implementation Working Group: Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential. Available online from 28 August 2020, end of consultation period 28 November 2020
[G] Anticipated Timeline for ICH 7SB guideline revision, New Approaches for an Integrated Nonclinical-Clinical QT/Proarrhythmic Risk Assessment, 15-16 October 2020