Cover Page

The handle [http://hdl.handle.net/1887/19939](http://hdl.handle.net/1887/19939) holds various files of this Leiden University dissertation.

**Author:** Chain, Anne S.Y.

**Title:** Mind the gap: predicting cardiovascular risk during drug development

**Date:** 2012-10-09
"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Winston Churchill
ACKNOWLEDGEMENTS

Forrest Gump's momma always said "Life was like a box of chocolates. You never know what you're gonna get." My life has certainly always been like a box of chocolate, especially during the past few years! Well, first I didn't always know I was going to go for a PhD and second, the journey has definitely been filled with both sweet and bittersweet moments.

I most certainly have to begin by acknowledging those who believed in me before I even realized this is what I wanted. Oscar, in the almost-ten years that I have known you, you've never failed to encourage me, to push me to my limits and beyond. You have not only expanded my world scientifically, but also culturally and gastronomically. You knew I would return to Leiden before I could imagine doing a second degree. I am truly lucky to have a champion like you on my side. But of course, this would not have been possible without the introduction from Meindert. Meindert, I will never forget the day I saw your picture on the Leiden University website. Albeit an unusual way to mark the start of one’s career, it's unlike sampling new chocolate based on attractive packaging. You have always given me the pivotal guidance and advice at the time of need. Your calm and no-nonsense mannerism have kept me focused and on track all the way to the finish line. And how can I go on without mentioning Dymphy, who was brave enough to take on the challenge to work with a rookie who knew absolutely nothing about modelling but a few ordinary differential equations.

Everyone at the division of Pharmacology has also made the experience that much sweeter. All the staff, post-docs and PhD colleagues have all been welcoming and accommodating. Much fond memories are made in and outside of the office with Rob, Liesbeth, Bert, Catherijne, Stina, Stephan, Massoud, Donato, Charlotte, Flora, Margot, Geert, Jaap, Maurice, Amit, Vincenzo, Vincent, Joost, Jasper, Chiara, Tarj, Roos, Massimo, Ashley, Francesco, Sven, Chantal, Imke, Marta, Erik, Bea, Linda, Iba and Elke. I will never forget our endless discussions on pharmacology, R, NONMEM, Dutch weather, Gorlaeus cafeteria, karnemelk, kroket and football. I will also be grateful for having wonderful students, Francesco and Morris, whom have worked so hard to help me execute a tremendously huge volume of simulations.
To be able to belong to another equally fun and stimulating group at the department of informatics in Erasmus Medical Centre has been nothing less than awesome. Miriam, I can still remember your glamorous entrance the first time I met you at the top of the stairs when you visited Leiden. You have been so supportive during my first encounters in the field of epidemiology and have continued to open doors to many opportunities and stuck by me throughout the last four years. Jeanne, I am very appreciative for your insights and patience. I have enjoyed our many discussions immensely. I am also grateful to belong to the same group as Jan, Ewout, Kris, Mees, Marcel, Carmen O., Tineke, Desiree, Rene, Bruno and proud to call Inge, Fatma, Roelof, Seppe, Eva, Emine, Alessandro, Ana, Ann, Vera, Sandra, Jelmer, Carmen F., Gianluca, Martijn, Silsana, Marius, Katia, Mendel, Charlotte, Eva van S., Eline, Toke, Rikje, Esben, Nico, Leo and Preci my friends.

Of course my project would not have been possible without the generosity from the Top Institute Pharma. Apart from the financial support, it has provided invaluable opportunities to collaborate with and learn from veterans in the field of pharmacology. I recognise the valuable interactions with Eliane Fuseau, Mats Karlsson, Andrew Hooker, David Spiegelhalter, David Lunn, Bronagh Heath, Nick McMahon, Jackie Bloomer, Piet Van Der Graaf, Mark Holbrook, John Davis, Dinesh de Alwis, Ivelina Gueorguieva, Charles Benson, Derek Leishman, An Vermeulen, David Gallacher, Rik de Greef, Thomas Kerbusch, Sandra Visser, Gezim Lahu, Axel Facius and Kevin Krudys who so kindly shared his expertise and his post-doctoral work as a starting point for this thesis.

My time in the Netherlands has also been enriched by Maren, Richie, Chrissy, Oli, Anna, Sandro, Nicole, Mike, Thomas, Andrew and David. Thank you for welcoming me into your lives and providing distractions for my "hard" time as a PhD student in Holland.

Having spent a combined two years as an undergraduate trainee and subsequently a graduate fellow at GlaxoSmithKline in London, I had the tremendous privilege to gain knowledge from and have fun with Abi, Pam, Isabelle, Daren, Bart, Gailing, Misba, Ann, Kevin S., Alex, Shuying, Sabrina, Claire, Guy, Alienor, Jonathan, Sophie, Alun, Stefano, Bela, Nicolas, Nadia, Chris, Georgios and Lorenzo. Hugo, who knew we would meet again under such different circumstances and in a different country. I will always be inspired by your constant attention to details and impeccable self-discipline.
Thank you for coming to my rescue and saved me from writing the Dutch Summary. Uncle Chao, your wisdom and constant life lessons have made me a better person today. Lutz, I shall never take for granted the foundation you have bestowed upon me and I can only hope to be able to continuously learn from you for many more years to come.

London has been much more than a learning experience. It has become a home away from home for the last few years with the generosity from Auntie Tessie, Norman, Daniel, Laura and Steve - you are my second family. My time there has also been filled with lasting memories, courtesy of Auntie Mary, Bryn, Auntie Sonia, Steve, Eva, Rashit, Nicole, Alan, Kevin, Claudia and Amy.

Being away from Toronto in the past few years has had its drawbacks. But I am very fortunate to have friends like Alyssa, Tom, Anthea, Mike, Anson, Jen, Ernest, Angela, Jeff, Luka, Karen, and Omar who never failed to satisfy my continuous cravings for sushi. Omar, a special note to you for all the design work you have put into this book and entertaining my relentless pursuit of nitty-gritty details - the colour grey will never be the same again.

My paranymphs, Elke and Preci - I cannot imagine surviving the last few years without you or share hotel rooms with anyone else around the world. Elke, you helped me navigate my way through life in Leiden and you were always the voice of reason when I was frustrated. Preci, my crazy twin sister, you always had a way to make me laugh and drive me crazy like nobody else can.

Auntie Meg, you have always reminded me that I can do whatever I want if I set my mind to it. I have become the self-reliant person I am today largely because of you. Mommy and daddy, you have given me a life full of opportunities and experiences that are unparalleled. You have trained me to always strive for excellence and never settle for mediocrity. I will always be grateful for the sacrifices you have made along the way and will forever be proud to be your daughter.

Finally, a big huge thank you to all those who I may have forgotten to mention. This journey would not have been as amazing without your friendships and unconditional support :)

Xoxo

Anne
PHD PORTFOLIO

Name          Anne S. Y. Chain
University     Leiden University, Division of Pharmacology
PhD Period    November 2007 - December 2011
Promotors     Prof. dr. Meindert Danhof,
              Prof. dr. Miriam C.J.M. Sturkenboom
Co-promotor   Dr. Oscar Della Pasqua

1. PHD TRAINING

Research Skills

2008          Advanced epidemiology course, Erasmus Winter Program
2008          Bayesian analysis, Reading University, UK
2008          ECG workshop, M&K courses, UK
2008          Six concepts to statistical thinking,
              Royal Statistical Society, UK
2008          Bayes Course, Cambridge University, UK
2009          Pharmacokinetic-pharmacodynamic modelling of continuous
              and categorical data in NONMEM,
              Uppsala Group, Washington DC, USA
2009          Binary and categorical data analysis, Leiden, The Netherlands
2010          Advanced R Course, Mango Solutions,
              Leiden, The Netherlands
2010          Drug Delivery Cycle, TI Pharma, The Netherlands
2010 Business and Entrepreneurial Skills, 
TI Pharma, The Netherlands

2011 R Graphics Course, Mango Solutions, San Diego, CA, USA

**Oral Presentations**

2009 *Not-In-Trial Simulation: Predicting Cardiovascular Risk from Clinical Trial Data.* European Association of Clinical Pharmacology and Therapeutics Meeting 2009, Edinburgh, United Kingdom.


2010 *Translating Cardiovascular Risk from Clinical Trial Data.* International Conference on Pharmacoepidemiology and Therapeutic Risk Management 2010, Brighton, United Kingdom.

**Poster Presentations**


2009 *Not-In-Trial Simulation: Predicting Cardiovascular Risk from Clinical Trial Data.* Population Approach Group Europe Meeting 2009, St. Petersburg, Russia.


2010 *QTc Prolongation Liability: Prospective Use of Not-In-Trial Simulations.* International Conference on Pharmacoepidemiology and Therapeutic Risk Management 2010, Brighton, United Kingdom.
<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
<th>Conference/Meeting</th>
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<tr>
<td>2011</td>
<td>Validation of a Not-In-Trial Simulation Tool for Cardiovascular Risk Mitigation.</td>
<td>International Conference on Pharmacoepidemiology and Therapeutic Risk Management 2011, Chicago, IL, USA.</td>
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**International Conferences**

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<th>Year</th>
<th>Conference/Meeting</th>
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<tr>
<td>2009</td>
<td>18th Population Approach Group Europe Meeting (PAGE) 23-26 June, 2009, St. Petersburg, Russia.</td>
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<tr>
<td>2009</td>
<td>25th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE). 16-19 August, Providence, Rhode Island, USA.</td>
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2010  19th Population Approach Group Europe Meeting (PAGE)  
    8-11 June, 2010, Berlin, Germany.

2010  26th International Conference on Pharmacoepidemiology and  
    Therapeutic Risk Management (ICPE).  9-22 August, 2010,  
    Brighton, United Kingdom.

2011  American Conference on Pharmacometrics (ACoP).  
    3-6 April, 2011, San Diego, California, USA.

2011  20th Population Approach Group Europe Meeting (PAGE)  
    7-10 June, 2011, Athens, Greece.

2011  27th International Conference on Pharmacoepidemiology and  
    Therapeutic Risk Management (ICPE).  14-17 August, 2011,  
    Chicago, Illinois, USA.

**Other Presentations and Seminars**

2008 - 2011  Leiden / Amsterdam Centre for Drug Research (LACDR)  
    Spring Symposiums.

2008 - 2011  TI Pharma Bi-annual Meetings.

2008 - 2011  Division of Pharmacology Lunchtime Seminars.

2008 - 2010  Research Colloquia in Medical Informatics, Department of  
    Medical Informatics, Erasmus University Medical Centre.

2009 - 2010  Medical Informatics Day, Erasmus University Medical Centre.

**2. TEACHING ACTIVITIES**

2007 - 2010  Teaching assistant to undergraduate students in  
    biopharmaceutical sciences.
    
    - Coordinated course logistics and assisted in mock clinical trials
    - Lectured on clinical trial designs and protocol writing
    - Conducted literature reviews with students
LIST OF PUBLICATIONS

• A.S.Y. Chain, K.M. Krudys, O. Della Pasqua. 
  *Clinical Pharmacology and Therapeutics, 2011 Dec; 90(6): 867-75.*

  Establishing in vitro to clinical correlations in the evaluation of cardiovascular safety pharmacology. 
  *Drug Discovery Today - Technologies, 2012. [In press]*

  Not-In-Trial Simulation I: Bridging Cardiovascular Risk from Clinical Trials to Real Life Conditions. 
  *British Journal of Clinical Pharmacology, 2012. [In press]*

  Simulating QT and RR Intervals for the Evaluation of Drug-Induced QTc-Interval Prolongation. 
  *British Journal of Clinical Pharmacology, 2012. [In press]*

  Population Pharmacokinetic Modelling of the Enterohepatic Recirculation of Diclofenac and Rofecoxib in Rats 
ABOUT THE AUTHOR

Anne S. Y. Chain was born on April 26th, 1982 in Hong Kong. Her family immigrated to Toronto, Ontario, Canada when she was 10 years old. In 2001, she completed high school as an Ontario Scholar award winner at North Toronto Collegiate Institute. She began Engineering Science at the University of Toronto in the same year, specializing in Biomedical Engineering in her third year of studies. In the summer of 2003, she was first introduced to pharmacokinetics modelling in a five-week traineeship at the Division of Pharmacology in Leiden University, under the guidance of Professor dr. Meindert Danhof and Dr. Oscar Della Pasqua. With the supervision of Ms. Dymphy Huntjens, she worked on a project involving enterohepatic recirculation of rofecoxib in rats and learnt the basic concepts of population compartmental modelling. Between 2004 and 2005, she continued on an industrial internship in Modelling and Simulation with Dr. Della Pasqua and Dr. Lutz Harnisch at GlaxoSmithKline, in London, United Kingdom as part of her undergraduate degree. While there, she was given the opportunity to evaluate the effect of d, l-sotalol on QT/QTc-interval prolongation in healthy volunteers. Anne graduated university with a Bachelors of Applied Science (BASc) degree in 2006.

Soon after graduation, Anne began working in Sapient Corporation, an international business consultancy in Toronto. In November 2007, she left her position as a senior associate in project management and returned to Leiden University to begin her PhD programme in cardiovascular safety. The research project described in this thesis is part of a work package belonging to the PKPD Modelling Platform within the Top Institute Pharma, a tripartite consortium, involving industry, academia and the Dutch government.

In the Spring of 2012, Anne joined the Modelling and Simulation group headed by Dr. Sandra Allerheiligen at Merck & Co. Inc. in Rahway, New Jersey, USA.
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AAI.</td>
<td>Arm ankle index</td>
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<tr>
<td>ADP.</td>
<td>Action potential duration</td>
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<td>ADR.</td>
<td>Adverse drug reaction</td>
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<td>BMI.</td>
<td>Body mass index</td>
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<td>CHMP.</td>
<td>Committee for Human Medicinal Products</td>
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<tr>
<td>CNS.</td>
<td>Central nervous system</td>
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<td>CPMP.</td>
<td>Committee for Proprietary Medicinal Products</td>
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<tr>
<td>CI.</td>
<td>Confidence interval</td>
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<td>CTS.</td>
<td>Clinical trial simulation</td>
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<td>CV.</td>
<td>Coefficient of variance</td>
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<td>CVS.</td>
<td>Cardiovascular safety</td>
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<td>DIC.</td>
<td>Deviance information criterion</td>
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<td>EAD.</td>
<td>Early after-depolarization</td>
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<td>ECG.</td>
<td>Electrocardiogram</td>
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<td>EMA.</td>
<td>European Medicine Agency</td>
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<td>FDA.</td>
<td>Food and Drug Administration</td>
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<td>GP.</td>
<td>General practitioners</td>
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<td>ICD.</td>
<td>International classification of diseases</td>
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<td>ICH.</td>
<td>International conference on harmonization</td>
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<td>MBDD.</td>
<td>Model-based drug discovery</td>
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<td>MCMC.</td>
<td>Markov chain Monte Carlo</td>
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<td>MEANS.</td>
<td>Modular ECG analysis system</td>
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<tr>
<td>MMRM.</td>
<td>Mixed model for repeated measure</td>
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<tr>
<td>NCE.</td>
<td>New chemical entities</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>NPDE.</td>
<td>Normalised prediction distribution error</td>
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<td>PKPD.</td>
<td>Pharmacokinetic-pharmacodynamic</td>
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<tr>
<td>QT.</td>
<td>Time interval between the Q and T peak in the electrocardiogram</td>
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<td>QTc.</td>
<td>Heart-rate corrected QT-interval</td>
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<tr>
<td>RBBB.</td>
<td>Right bundle-branch block</td>
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| RR.          | 1. Relative risk  
               2. Time interval between successive R peaks in the electrocardiogram |
| SCD.         | Sudden cardiac death |
| TdP.         | Torsade de pointes |
| TQT.         | Thorough-QT |
| VPC.         | Visual predictive check |
| WHO.         | World health organization |
STELLINGEN / PROPOSITIONS TO THIS DISSERTATION

1. A major gap in the evaluation of cardiovascular safety is the reliance on empirical evidence. *This thesis*

2. The predictive power of the techniques and methodologies currently available for the evaluation of cardiovascular risk depends upon careful consideration of the clinically relevant conditions. *This thesis*

3. The use of model parameterisation discriminating drug- and system-specific properties eliminates the bias arising from the current regulatory guidelines. *This thesis*

4. The integration of pharmacological concepts with pharmaco-epidemiology offers a unique opportunity to bridge the gap between clinical trials and real life conditions. *This thesis*

5. The concept of Not-In-Trial Simulations defies the hurdles imposed by the evidentiary axiom “the absence of evidence is not evidence of absence”. *This thesis*

6. The possibility to communicate QTc prolongation in terms of probability provides transparency that greatly enhances the decision-making processes throughout drug development. *This thesis*

7. The marked differences observed between clinical trials and post-marketing use confirm that pre- and post-approval are two distinct worlds. *(Martin, K. et al., Br J Clin Pharmacol 2003; 57: 86–92)*

8. The most important- and vexing- questions in clinical cardiology today can be phrased quite simply: “‘Why did he die on Tuesday and not on Monday?’ If we can identify the transient initiating event, we can begin to develop more effective strategies for prevention of SCD. *(Rubart M. & Zipes D.P., JCI 2005;115(9):1–11)*

9. In order to make a fully informed treatment decision, it is logical that all available information be used. *(Lynd L.D. & O’Brien B.J., J Clin Epidemiol 2004; 57: 795–803)*
10. The forecast is that complex, mixed-effects, mechanistic PD models combined with Bayesian estimation and incorporating different sources of prior knowledge will provide a paradigm for future model development. (Csajka C. & Verotta D., JPP 2006; 33: 227-279)

11. Even a Nobel laureate can be wrong. Today Carrel would not have stated that, "a few observations and much reasoning lead to error; many observations and a little reasoning to truth." ~Alexis Carrel, Nobel Prize winner, 1912.

12. The phrase "mind the gap" has never been so applicable to the pharmaceutical industry as in the last five years. The gaps in the drug development process are larger than those on any train platform.