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The human dimension in the assessment of medicines

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7.1

ACKNOWLEDGEMENTS

‘Writing a book is a horrible, exhausting struggle, like a long bout of some painful illness.’ So wrote George Orwell in 1946. I wholeheartedly concur but would substitute ‘thesis’ for ‘book’. This struggle, however, was made bearable by the collective contributions of so many that it may be difficult to enumerate.

First, my thanks to my promoters Pieter de Graeff and Hans Hillege for supporting my secondment to the European Medicines Agency to participate in the EMA Benefit Risk (BR) Methodology Project. They provided the freedom for me to pursue the direction I wished to take for the thesis and for that they have my unending gratitude. The objectives of the project and the opportunity for seeing first-hand how medicines are regulated in Europe provided an invaluable learning experience. Next, my thanks go to Hans-Georg Eichler, who in his role as Senior Medical Officer of the EMA took a great deal of interest in the development of my thesis and provided a sounding board for my ideas and frustrations and giving valuable advice. I also owe him a huge debt of gratitude for suggesting that I pursue the development of a model that would support the representative interaction of patients in the regulatory process, and it is worth saying that without his encouragement my thesis would not have taken this particular direction.

Then there is Professor Larry Phillips of the London School of Economics and Political Science (LSE). I owe so much to Larry. As leader of the EMA BR Methodology Project, he set the standard of academic achievement that was expected from anyone purporting to participate in the project and always pushed me to go further and dig deeper. He has worked with many of the giants in the field of behavioural psychology, behavioural economics and decision theory, and each conversation with him was an education in itself. My determination to prove myself and my scholarship worthy in his eyes was a major driving force in the completion of this thesis. Many thanks also go to Professor Barbara Fasolo, also from the LSE, who was the first to read my proposals on risk perception among the assessors and say ‘you are going in a good direction’. Her calm manner and positive outlook coupled with her deep knowledge of the field of risk research were invaluable during the years in which we worked together on the EMA BR Methodology Project.

I can truly say that it has been a pleasure to work with Professor Carlos Bana e Costa. During the writing of a paper we co-authored, he once said ‘At the end of this you will either love me or hate me’. Needless to say, I do not hate Carlos; he is a scholar extraordinaire and has spent countless hours explaining the intricacies of the MACBETH approach and supporting the development of the VALUE study questionnaire to capture patient preferences. Together, he and Joao Bana e Costa have put in countless hours to support the programming required to create a user interface linked to the MACBETH software, with Joao sometimes sleeping only a few hours a day to meet the timelines. They both have my immense gratitude.

A special thought for my family and friends, named and unnamed, who suffered my physical absence at family gatherings and weekends while I completed this thesis. To friends who read endless drafts and rewrites and provided helpful comments to improve the clarity of my writing, my deep and sincere gratitude. Big thanks to Ettore and his parents Bruna and Giuseppe Brambilla; you provided me with the love and encouragement I needed each time I came home to Italy weary from travel and the demands of juggling life and work in London. To my mother and my belated father, Vera and Raymond Phillips, you have both, in different ways, inspired me to excel at whatever task I undertake; thank you for laying that foundation early in my life. Thanks to Enrica Alteri who, as a friend for many years and more recently a colleague at the EMA, has been support personified, always ready with a quick hug and an encouraging word. Thanks to Marisa Bacchi, my friend and previous supervisor, who always supported my aspirations and was my big champion when I decided to leave my job and embark on an academic career and who always let me know that there was a place for me whenever I wished to return. Thanks for that safety net. There were many times during the years when my hands hovered over the phone, but I resisted, as I knew you would be there whenever I was ready.

To Xavier Kurz, the EMA Lead for the IMI-PROTECT project who after observing my research progress at EMA exhibited his confidence in me by supporting the application of a grant to lead a study under the IMI-PROTECT WP6. The combination of the final year of my thesis coupled with the launch of the VISUALizE study was a perfect example of work-life imbalance and I would discourage anyone attempting to repeat the experience. However, by surviving this period, my confidence in my ability to make meaningful contributions to my chosen area of research increased tenfold. Support at this level is usually reserved for full professors, and I am humbled that Xavier sufficiently valued my work to support the ascension of UMCG to the IMI-PROTECT project. The study has been a success and I anticipate that we have enough data for at least eight or ten publications.

My thanks to the medical assessors in the participating National Competent Agencies who persevered through the completion of a 45-page questionnaire. This thesis would really not have been possible if they had not taken the hours and days needed to provide the data. It has been years now since the first questionnaire was launched, so the huge block of chocolate that each assessor received has probably faded in their memory, and so I reiterate my thanks here. Lastly, to the UK Multiple Sclerosis Society and the patients who participated in the VALUE study, you were the first to provide data for this application of the redesigned M-MACBETH. Thank you, not only for contributing to this current work but also for the continued struggle both at the organizational level and at the individual level to let the voice of the patients be heard at all points of the development of a drug. It

seems, with the advent of the recent IMI call for a project on how to involve patients in regulatory decision making, that the powers to be have heard you and the momentum is growing. Keep pushing, and I'll be there to push with you.

7.2

LIST OF CO-AUTHORS

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7.3

LIST OF PUBLICATIONS

Beyer A, Fasolo B, Hillege H, de Graeff P. Risk attitudes and personality traits as predictors of the benefit-risk assessment for medicinal products: a psychological evaluation of European medical assessors. *Value in Health* 2015 Jan; 18(1):91-9.

Beyer A, Fasolo B, Phillips L, Hillege H, de Graeff P. Risk Perception of Prescription Drugs: Results of a survey among experts in the European Regulatory Network. *Medical Journal of Decision Making*, published online 11 March 2013;33(4): 579-592.

Phillips L, Fasolo B, Zafiroplous N, Beyer A. Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discovery Today* 2011;8(1):3-10

Beyer A, de Graeff P, Hillege H. Assessing Importance Of To Clinical Trial Data In A Marketing Dossier: Where Do Assessors Place Their Value? Submitted for publication.

Beyer A, Bana e Costa C, Fasolo B, de Graeff P, Hillege H, Eichler HG. Values among multiple sclerosis patients: application of a decision-analytic tool to the elicitation of preferences for treatment outcomes. Submitted for publication.

Beyer A, Phillips L, de Graeff P, Hillege H. Values Among European Regulators And Patients: Applying The Macbeth Approach To Decision Making For Multiple Sclerosis Treatments. Submitted for publication.

Scientific publications not included in this thesis

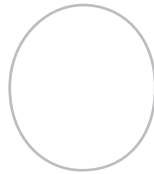
Mühlbacher A, Juhnke C, Beyer A, Garner S. Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European perspective. Submitted for publication.

Annesi-Maesano I, Beyer A, Marmouz F, Mathelier-Fusade P, Vervloet D, & Bauchau V. Concurrent allergic disease: a cross-sectional study in a French population. *Allergy* 2006; 61:390-1.

Annesi-Maesano I, Beyer A, Marmouz F, Mathelier-Fusade P, Vervloet D, & Bauchau V. Do patients with skin allergies have higher levels of anxiety than patients with allergic respiratory disease? Epidemiological evidence for psychological symptoms and skin disease. *British Journal of Dermatology*; 2006;154:1128-1136.



ABOUT THE AUTHOR



Andrea was born in St Thomas, Jamaica and immigrated to New York with her parents and siblings in 1983. She graduated Magna Cum Laude from Spelman College in Atlanta, Georgia in 1995 where she was the 1994 recipient of the Dewitt Wallace Scholarship and obtained a Bachelor's degree in Political Science and Biology. Andrea completed her Master's degree in Public Health from Emory University, Atlanta and wrote her Master's thesis on the increase risk of very low birth weight infants among African American women '*Very Low Birth Weight Infants of Black and White College Graduates*'. Since completing her MPH Andrea has worked as an Epidemiologist conducting research funded by the Centres for Disease Control (CDC), Family Health International and the Rollins School of Public Health. In 2001, after relocating to the UK, she worked as a Statistical Epidemiologist for several pharmaceutical companies. From August 2009 to 2013 she worked on the studies presented in this thesis as a PhD student in the Department of Epidemiology, the Research Institute SHARE of the University of Groningen (UMCG). During the first year of the PhD program Andrea was seconded as a national expert under a collaborative agreement with the UMCG and the European Medicines Agency. The studies presented in this thesis were conducted within the framework of the EMA Benefit-Risk Methodology project and under the supervision of Prof. P.A. de Graeff and Prof. H. Hillege. In parallel she was a Visiting Research Student at the London School of Economics and Political Science where she worked closely with Prof. B. Fasolo. In January 2013 she was successful in securing the ascension of the UMCG to the IMI-PROTECT project and has provided leadership for the IMI-PROTECT WP6 study Visualising Uncertainty Among Laypersons and Experts (VISUALizE), designed to collect data across three European countries on extending benefit-risk methodologies to patients, healthcare professionals and European medical assessors.

The image features large, hollow outline numbers '7.5' in a light gray color. The number '7' is on the left, followed by a period, and then the number '5' on the right. The text 'LIST OF SHARE DISSERTATIONS' is centered horizontally between the '7' and the '5', positioned slightly above the baseline of the numbers.

LIST OF SHARE DISSERTATIONS

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This thesis is published within the **Research Institute SHARE** (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen.

Further information regarding the institute and its research can be obtained from our internetsite: <http://www.share.umcg.nl/>

More recent theses can be found in the list below.

((co-) supervisors are between brackets)

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Meijer MF

Innovations in revision total knee arthroplasty
(*prof SK Bulstra, dr M Stevens, dr IHF Reininga*)

Pitman JP

The influence and impact of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) on blood transfusion in Africa; case studies from Namibië
(*Prof MJ Postma, prof TS van der Werf*)

Scheppingen C van

Distress and unmet needs in cancer patients; challenges in intervention research
(*prof R Sanderman, dr G Pool, dr MJ Schroevers*)

Bouwman II

Lower urinary tract symptoms in older men: does it predict the future?
(*prof K van der Meer, prof JM Nijman, dr WK van der Heide*)

Geurts, MME

Integrated pharmaceutical care; cooperation between pharmacist, general practitioner, and patient and the development of a pharmaceutical care plan
(*prof JJ de Gier, prof JRB Brouwers, prof PA de Graeff*)

Sun J

Developing comprehensive and integrated health system reform policies to improve use of medicines in China
(*prof HV Hogerziel, prof SA Reijneveld*)

Wyk, L van

Management of term growth restriction; neonatal and long term outcomes
(*prof SA Scherjon, prof JMM van Lith, dr KE Boers, dr S le Cessie*)

Vos FI

Ultrasonography of the fetal nose, maxilla, mandible and forehead as markers for aneuploidy
(*prof CM Bilardo, prof KO Kagan, dr EAP de Jong-Pleij*)

Twillert S van

Linking scientific and clinical knowledge practices; innovation for prosthetic rehabilitation
(*prof K Postema, prof JHB Geertzen, dr A Lettinga*)

Loo HM van

Data-driven subtypes of major depressive disorder
(*prof RA Schoevers, prof P de Jonge, prof JW Romeijn*)

Raat AN

Peer influence in clinical workplace learning; a study of medical students' use of social comparison in clinical practice
(*prof J Cohen-Schotanus, prof JBM Kuks*)

Standaert BACGM

Exploring new ways of measuring the economic value of vaccination with an application to the prevention of rotavirus disease
(*prof MJ Postma, dr O Ethgen*)

Kotsopoulos N

Novel economic perspectives on prevention and treatment: case studies for paediatric, adolescent and adult infectious diseases
(*prof MJ Postma, dr M Connolly*)

Feijen-de Jong, EI

On the use and determinants of prenatal healthcare services
(*prof SA Reijneveld, prof F Schellevis, dr DEMC Jansen, dr F Baarveld*)

Hielkema M

The value of a family-centered approach in preventive child healthcare
(*prof SA Reijneveld, dr A de Winter*)

Dul EC

Chromosomal abnormalities in infertile men and preimplantation embryos
(*prof JA Land, prof CMA van Ravenswaaij-Arts*)

Heeg BMS

Modelling chronic diseases for reimbursement purposes
(*prof MJ Postma, prof E Buskens, prof BA van Hout*)

Vries, ST de

Patient perspectives in the benefit-risk evaluation of drugs
(*prof P Denig, prof FM Haaijer-Ruskamp, prof D de Zeeuw*)

Zhu L

Patterns of adaptation to cancer during psychological care
(*prof AV Ranchor, prof R Sanderman, dr MJ Schroevers*)

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Vart P

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Kolvek G

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Mikula P

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(prof RMH Schaub, prof JW Groothoff, prof N Widyanti)

Christoffers WA

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