

DATA MONITORING *in* CLINICAL TRIALS

A Case Studies Approach

David L. DeMets
Curt D. Furberg
Lawrence M. Friedman
Editors



Springer

Contents

Preface	v
Contributors	ix

Section 1: Introduction/Overview

1	Monitoring Committees: Why and How	3
	<i>David L. DeMets</i>	
	<i>Curt D. Furberg</i>	
	<i>Lawrence M. Friedman</i>	
2	Lessons Learned	14
	<i>David L. DeMets</i>	
	<i>Curt D. Furberg</i>	
	<i>Lawrence M. Friedman</i>	
3	FDA and Clinical Trial Data Monitoring Committees	39
	<i>Susan S. Ellenberg</i>	
	<i>Jay P. Siegel</i>	

Section 2: General Benefit

	Introduction to Case Studies Showing Benefit From the Intervention	53
	<i>David L. DeMets</i>	
	<i>Curt D. Furberg</i>	
	<i>Lawrence M. Friedman</i>	
Case 1	Assessing Possible Late Treatment Effects Early: The Diabetic Retinopathy Study Experience	55
	<i>Fred Ederer</i>	
Case 2	Data and Safety Monitoring in the Beta- Blocker Heart Attack Trial: Early Experience in Formal Monitoring Methods	64
	<i>Lawrence M. Friedman</i>	
	<i>David L. DeMets</i>	
	<i>Robert Hardy</i>	

Case 3	Data Monitoring for the Aspirin Component of the Physicians' Health Study: Issues in Early Termination for a Major Secondary Endpoint	73
	<i>David L. DeMets</i> <i>Charles H. Hennekens</i>	
Case 4	Early Termination of the Stroke Prevention in Atrial Fibrillation I Trial: Protecting Participant Interests in the Face of Scientific Uncertainties and the Cruel Play of Chance	85
	<i>Robert G. Hart</i> <i>Lesly A. Pearce</i> <i>Ruth McBride</i> <i>Richard A. Kronmal</i>	
Case 5	Early Termination of the Diabetes Control and Complications Trial	93
	<i>John M. Lachin</i> <i>Patricia Cleary</i> <i>Oscar Crofford</i> <i>Saul Genuth</i> <i>David Nathan</i> <i>Charles Clark</i> <i>Frederick Ferris</i> <i>Carolyn Siebert</i> <i>for the DCCT Research Group</i>	
Case 6	Data Monitoring in the AIDS Clinical Trials Group Study #981: Conflicting Interim Results	109
	<i>Dianne M. Finkelstein</i>	
Case 7	Challenges in Monitoring the Breast Cancer Prevention Trial	118
	<i>Carol K. Redmond</i> <i>Joseph P. Costantino</i> <i>Theodore Colton</i>	
Case 8	Data Monitoring Experience in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure: Potentially High-Risk Treatment in High-Risk Patients	136
	<i>Jan Feyzi</i> <i>Desmond Julian</i> <i>John Wikstrand</i> <i>Hans Wedel</i>	

Case 9	Stopping the Randomized Aldactone Evaluation Study Early for Efficacy	148
	<i>Janet Wittes</i>	
	<i>Jean-Pierre Boissel</i>	
	<i>Curt D. Furberg</i>	
	<i>Desmond Julian</i>	
	<i>Henri Kulbertus</i>	
	<i>Stuart Pocock</i>	
Case 10	Data Monitoring in the Heart Outcomes Prevention Evaluation and the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trials: Avoiding Important Information Loss	158
	<i>Janice Pogue</i>	
	<i>David Sackett</i>	
	<i>DG Wyse</i>	
	<i>Salim Yusuf</i>	
Case 11	The Data Monitoring Experience in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Program	166
	<i>Stuart Pocock</i>	
	<i>Duolao Wang</i>	
	<i>Lars Wilhelmsen</i>	
	<i>Charles H. Hennekens</i>	

Section 3: General Harm

	Introduction to Case Studies Showing Harmful Effects of the Intervention	179
	<i>David L. DeMets</i>	
	<i>Curt D. Furberg</i>	
	<i>Lawrence M. Friedman</i>	
Case 12	Breaking New Ground: Data Monitoring in the Coronary Drug Project	183
	<i>Paul L. Canner</i>	
Case 13	The Data Monitoring Experience in the Cardiac Arrhythmia Suppression Trial: The Need To Be Prepared Early	198
	<i>David L. DeMets</i>	
	<i>Lawrence M. Friedman</i>	

Case 14	Data Monitoring in the Prospective Randomized Milrinone Survival Evaluation: Dealing with an Agonizing Trend	209
	<i>Susan Anderson</i> <i>Robert Cody</i> <i>Milton Packer</i> <i>Richard Schwarz</i>	
Case 15	Stopping the Carotene and Retinol Efficacy Trial: The Viewpoint of the Safety and Endpoint Monitoring Committee	220
	<i>Anthony B. Miller</i> <i>Julie Buring</i> <i>O. Dale Williams</i>	
Case 16	Monitoring a Clinical Trial With Waiver of Informed Consent: Diaspirin Cross-Linked Hemoglobin for Emergency Treatment of Post-Traumatic Shock	228
	<i>Roger J. Lewis</i> <i>Norman Fost</i>	
Case 17	Consideration of Early Stopping and Other Challenges in Monitoring the Heart and Estrogen/Progestin Replacement Study	236
	<i>Stephen B. Hulley</i> <i>Deborah Grady</i> <i>Eric Vittingboff</i> <i>O. Dale Williams</i>	
Case 18	Data Monitoring in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: Early Termination of the Doxazosin Treatment Arm	248
	<i>Barry R. Davis</i> <i>Jeffrey A. Cutler</i>	
Case 19	Data Monitoring Experience in the Moxonidine Congestive Heart Failure Trial	260
	<i>Stuart Pocock</i> <i>Lars Wilhelmsen</i> <i>Kenneth Dickstein</i> <i>Gary Francis</i> <i>Janet Wittes</i>	

Case 20	Data Monitoring of a Placebo-Controlled Trial of Daclizumab in Acute Graft-Versus-Host Disease	269
	<i>David Zahrieh</i>	
	<i>Stephanie J. Lee</i>	
	<i>David Harrington</i>	

Section 4: Special Issues

	Introduction to Case Studies With Special Issues	281
	<i>David L. DeMets</i>	
	<i>Curt D. Furberg</i>	
	<i>Lawrence M. Friedman</i>	
Case 21	Clinical Trials of Herpes Simplex Encephalitis: The Role of the Data Monitoring Committee	285
	<i>Richard J. Whitley</i>	
Case 22	The Nocturnal Oxygen Therapy Trial Data Monitoring Experience: Problem With Reporting Lags	292
	<i>David L. DeMets</i>	
	<i>George W. Williams</i>	
	<i>Byron W. Brown, Jr.</i>	
Case 23	Stopping a Trial for Futility: The Cooperative New Scandinavian Enalapril Survival Study II	302
	<i>Steven Snapinn</i>	
	<i>Curt D. Furberg</i>	
Case 24	Lessons From Warfarin Trials in Atrial Fibrillation: Missing the Window of Opportunity	312
	<i>Charles H. Tegeler</i>	
	<i>Curt D. Furberg</i>	
Case 25	Data Monitoring Experience in the AIDS Toxoplasmic Encephalitis Study	320
	<i>James D. Neaton</i>	
	<i>Deborah N. Wentworth</i>	
	<i>Mark A. Jacobson</i>	

Case 26	Data Monitoring in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study: When Reasonable People Disagree	330
	<i>Janice Pogue</i> <i>Salim Yusuf</i>	
Case 27	The Data Monitoring Experience in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study: Hazards of Changing Primary Outcomes	337
	<i>Desmond Julian</i>	
Case 28	Controversies in the Early Reporting of a Clinical Trial in Early Breast Cancer	346
	<i>Stephen L. George</i> <i>Mark R. Green</i>	
Case 29	Making Independence Work: Monitoring the Bevacizumab Colorectal Cancer Clinical Trial	360
	<i>Janet Wittes</i> <i>Eric Holmgren</i> <i>Heidi Christ-Schmidt</i> <i>Alex Bajamonde</i>	
Appendix 1	Data Monitoring Committee Members	368
Appendix 2	Case Study Acronym Key (Title)	371
Index		372