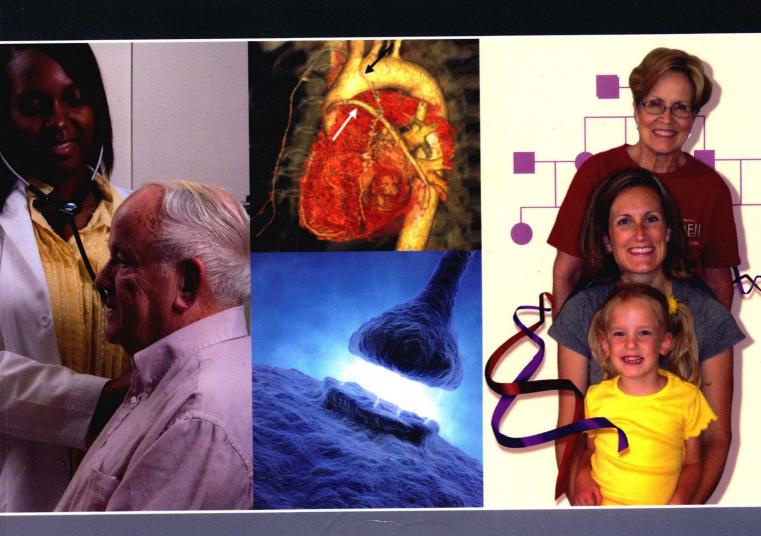
## CLINICAL AND TRANSLATIONAL SCIENCE:

PRINCIPLES OF HUMAN RESEARCH



Edited by
David Robertson
Gordon H. Williams



# Clinical and Translational Science

Principles of Human Research

## Second Edition

### Edited by

#### David Robertson MD

Director, Clinical & Translational Research Center, Elton Yates Professor of Medicine, Pharmacology and Neurology, Vanderbilt University, Nashville, TN, United States

#### Gordon H. Williams MD

Chief, Hormonal Mechanisms of Cardiovascular Injury Laboratory, Brigham and Women's Hospital, and Professor of Medicine, Harvard Medical School, Boston, MA, United States





Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2017 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

#### **Notices**

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

#### Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

#### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-802101-9

For information on all Academic Press publications visit our website at https://www.elsevier.com/



www.elsevier.com • www.bookaid.org

Publisher: Mica Haley

Acquisition Editor: Mica Haley

Editorial Project Manager: Lisa Eppich Production Project Manager: Laura Jackson

Designer: Victoria Pearson Esser

Typeset by TNQ Books and Journals

## **List of Contributors**

- Salim Abdool Karim University of KwaZulu—Natal, Durban, South Africa; Columbia University, New York, NY, United States
- **Donna K. Arnett** University of Kentucky, Lexington, KY, United States
- James R. Baker, Jr. University of Michigan, Ann Arbor, MI, United States
- **Seema Basu** Partners HealthCare Innovation, Cambridge, MA, United States
- Stacey Berg Texas Children's Hospital, Houston, TX, United States
- **Gordon R. Bernard** Vanderbilt University School of Medicine, Nashville, TN, United States
- Italo Biaggioni Vanderbilt University, Nashville, TN, United States
- Lisa Bomgaars Texas Children's Hospital, Houston, TX, United States
- **Robert A. Branch** University of Pittsburgh, Pittsburgh, PA, United States
- Nancy J. Brown Vanderbilt University School of Medicine, Nashville, TN, United States
- **Robert M. Califf** U.S. Food and Drug Administration, Silver Spring, MD, United States
- **Henry C. Chueh** Massachusetts General Hospital, Boston, MA, United States
- Steven A. Claas University of Alabama at Birmingham, Birmingham, AL, United States
- William F. Crowley, Jr. Massachusetts General Hospital, Boston, MA, United States
- Joann Data Data Consulting, Sparta, TN, United States
- **George D. Demetri** Dana-Farber Cancer Institute and Ludwig Center at Harvard, Harvard Medical School, Boston, MA, United States
- **Zeruesenay Desta** Indiana University, Indianapolis, IN, United States
- Ruth M. Dunne Harvard Medical School, Boston, MA, United States

- Luigi Ferrucci NIA, Baltimore, MD, United States
- **David A. Flockhart** Indiana University, Indianapolis, IN, United States
- **Audrey Gassman** U.S. Food and Drug Administration, Silver Spring, MD, United States
- Rashmi Gopal-Srivastava National Institutes of Health, Bethesda, MD, United States
- Glenn Gormley Daiichi Sankyo Inc., Edison, NJ, United States
- Steven Grinspoon Harvard Medical School, Boston, MA, United States
- **Stephen C. Groft** National Institutes of Health, Bethesda, MD, United States
- **Katherine E. Hartmann** Vanderbilt University School of Medicine, Nashville, TN, United States
- **Elizabeth Heitman** Vanderbilt University School of Medicine, Nashville, TN, United States
- Christopher D. Herrick Massachusetts General Hospital, Boston, MA, United States
- **Hylton V. Joffe** U.S. Food and Drug Administration, Silver Spring, MD, United States
- **Kush Kapur** Harvard Medical School, Boston, MA, United States
- Mark D. Kellogg Boston Children's Hospital, Boston, MA, United States
- **Richard B. Kim** The University of Western Ontario, London, ON, Canada
- **Bruce R. Korf** University of Alabama at Birmingham, Birmingham, AL, United States
- Greg Koski Harvard Medical School, Boston, MA, United States; Massachusetts General Hospital, Boston, MA, United States
- Ronald L. Krall University of Pittsburgh, Pittsburgh, PA, United States; GlaxoSmithKline
- Jessica Lasky-Su Harvard Medical School and Brigham and Women's Hospital, Boston, MA, United States

- Shawn N. Murphy Massachusetts General Hospital, Boston, MA, United States
- Christine Nguyen U.S. Food and Drug Administration, Silver Spring, MD, United States
- Ailbhe C. O'Neill Harvard Medical School, Boston, MA, United States
- Daniel J. Pallin Harvard Medical School, Boston, MA, United States
- James Quinn Stanford University, Stanford, CA, United
- Keren Regev Harvard Medical School, Boston, MA, United States
- Uwe E. Reinhardt Princeton University, Princeton, NJ, United States
- Todd W. Rice Vanderbilt University School of Medicine, Nashville, TN, United States
- Rose Marie Robertson American Heart Association, Dallas, TX, United States
- David Robertson Clinical & Translational Research Center, Elton Yates Professor of Medicine, Pharmacology and Neurology, Vanderbilt University, Nashville, TN,
- Dan M. Roden Vanderbilt University Medical Center, Nashville, TN, United States
- Angela J. Rogers Stanford University, Stanford, CA, **United States**
- Daniel E. Salazar EMS Pharma, Hortolàndia, SP, Brazil
- J. Sanford Schwartz University of Pennsylvania, Philadelphia, PA, United States
- Alan F. Schatzberg Stanford University, Stanford, CA, **United States**
- Ellen W. Seely Harvard Medical School, Boston, MA, **United States**
- Joe V. Selby Patient-Centered Outcomes Research Institute, Washington, DC, United States
- César Serrano Vall d'Hebron University Hospital, Barcelona, Spain

- **Donald C. Simonson** Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
- Ann R. Stark Monroe Carell Jr. Children's Hospital, Nashville, TN, United States
- Stephanie Studenski NIA, Baltimore, MD, United States
- Clare M. Tempany Harvard Medical School, Boston, MA, United States
- Marcia A. Testa Harvard T. H. Chan School of Public Health, Boston, MA, United States
- **Thommey P. Thomas** University of Michigan, Ann Arbor, MI, United States
- Rommel G. Tirona The University of Western Ontario, London, ON, Canada
- Stephanie L. Tomasic The Pitt-Bridge: Gateway to Success, Pittsburgh, PA, United States
- Suzie Upton American Heart Association, Dallas, TX, United States
- Sten H. Vermund Vanderbilt University, Nashville, TN, United States
- Brent B. Ward University of Michigan, Ann Arbor, MI, United States
- Howard L. Weiner Harvard Medical School, Boston, MA, United States
- Scott T. Weiss Harvard Medical School, Boston, MA, United States; Partners HealthCare Personalized Medicine, Boston, MA, United States; Channing Division of Network Medicine, Boston, MA, United States
- $\mathbf{M}$ . Whicher Patient-Centered Outcomes Research Institute, Washington, DC, United States
- Gordon H. Williams Hormonal Mechanisms of Cardiovascular Injury Laboratory, Brigham and Women's Hospital, and Professor of Medicine, Harvard Medical School, Boston, MA, United States
- Mary Woolley Research! America, Alexandria, VA, United
- Nathalie K. Zgheib American University of Beirut, Beirut, Lebanon

## Contents

List of Contributors	xix		Conclusions References	21 21
Section I		3.	Clinical Trials	
Fundamental Principles			Robert M. Califf	
			Introduction	26
1. Introduction to Clinical Research			History	26
Gordon H. Williams and David Robertson			Phases of Evaluation of Therapies	26
Historical Background	3		Critical General Concepts Purposes of Clinical Trials	27 27
Organization of This Book	6		Validity	27
Note	6		Generalizability	28
References	7		Trade-off of Validity and Generalizability	28
	,		Expressing Clinical Trial Results	29
2. Patient-Oriented Research			Concepts Underlying Trial Design	30
			Treatment Effects Are Modest	31
Ellen W. Seely and Steven Grinspoon			Qualitative Interactions Are Uncommon	32
Introduction	9		Quantitative Interactions Are Common	32
Types of Patient-Oriented Research	10		Unintended Biological Targets Are Common	32
Observational Studies	11		Interactions Among Therapies Are Not	
Mechanism Studies	11		Predictable	33
Therapeutic Studies	12		Long-Term Effects May Be Unpredictable	33
Clinical Trials	12		General Design Considerations	33
The Role of Patient-Oriented Research in			Pragmatic Versus Explanatory	34
Translational Research	14		Entry Criteria	34
Interaction of Basic Science and Patient-			Data Collection Instrument	34
Oriented Research	14		Ancillary Therapy and Practice	35
Interaction of Patient-Oriented Research and			Multiple Randomization	35
the Community	15		Adaptive Trial Designs	35
The Role of the Patient in Patient-Oriented			Legal and Ethical Issues	36
Research	15		Medical Justification	36
Sequence of Investigation	16		Groups of Patients Versus Individuals	36
Hypothesis Generation	16		Blinding	37
Designing the Study	16		Endpoint Adjudication	37
Feasibility	19		Intensity of Intervention	38
Confounding	19		Surrogate Endpoints	38
Subject Safety and the Institutional Review	4.0		Conflict of Interest	38
Board	19		Special Issues With Device Trials	39
Database Development	20		Hypothesis Formulation	40
Data Analysis Plan Tools of the Patient Oriented Researcher	20		Primary Hypothesis	40
Tools of the Patient-Oriented Researcher Funding for Patient-Oriented Research	20 21		Secondary and Tertiary Hypotheses	40 41
runding for ratient-Offented Kesearch	/		intendon to freat	4

	Publication Bias	41 41	5.	The Patient-Centered Outcomes	
	Statistical Considerations	41		Research Institute: Current Approach	
	Type I Error and Multiple Comparisons	41		to Funding Clinical Research and	
	Type II Error and Sample Size	42		Future Directions	
	Noninferiority Sample Size Calculations	42		Joe V. Selby and Danielle M. Whicher	
	Metaanalysis and Systematic Overviews	43		Introduction: The Patient-Centered Outcomes	
	Understanding Covariates and Subgroups	44			72
	Therapeutic Truisms	44		Research Institute	12
	Study Organization	45		Patient-Centered Comparative Effectiveness	73
	Executive Functions	45		Research Defining Patient-Centered Comparative	13
	Coordinating Functions	47		Effectiveness Research	73
	Supporting Functions	47			13
	Integration Into Practice	49		Establishing National Priority Areas for	
	The Future	49		Patient-Centered Comparative Effectiveness	74
	Acknowledgment	50		Research  Retient and Stakeholder Engagement in	/4
	References	50		Patient and Stakeholder Engagement in	74
	The form of the fo			Research	/4
4	Introduction to Epidemiology			PCORI's Efforts to Engage Patients and Stakeholders in Setting Research Priorities	
•	•			and Selecting Research Applications for	
	Donna K. Arnett and Steven A. Claas				74
	Introduction: Definition and Role of			Funding Engaging Patients and Stakeholders in	7 4
	Epidemiology	54		Conducting Research	75
	Measuring Occurrence of Disease	55		PCORI's Rubric for Patient and Stakeholder	13
	Defining Diseases, Outcomes, and Other			Engagement	76
	Health-Related States or Events	55		Methodology Standards for Patient-Centered	70
	Calculating Incidence and Prevalence	56		Comparative Effectiveness Research	77
	Measuring Risk and Association	57		PCORI's Methodology Committee	77
	Calculating Risk	57		PCORI's Methodology Standards	77
	Quantifying Associations	58		Pragmatic Research	78
	Types of Epidemiological Studies	59		Defining Features of Pragmatic Research	78
	Cross-sectional Studies	59		PCORI's Efforts to Support Pragmatic	, 0
	Cohort Studies	59		Research	78
	Case—Control Studies	60		Study Designs for Pragmatic Research	, 0
	Hybrid Study Designs	61		and Other Comparative Effectiveness	
	Study Design: Summary	62		Research	80
	Threats to Validity and Reliability	62		Integrating Research Into the Learning	
	Defining and Measuring Threats to Validity			Health-Care System	81
	and Reliability	62		The Case for Locating Clinical Research	
	Estimating and Avoiding Threats to Validity	64		Within Health-Care Delivery	81
	Estimating and Avoiding Threats to Reliability	65		Electronic Health Records and Insurance	
	Moving From Association to Causation	65		Claims Data	81
	Clinical Epidemiology	67		The Use of Clinical Registries in Research	82
	Sex, Gender, Race, and Ethnicity in			The National Patient-Centered Outcomes	
	Epidemiology	67		Research Network	83
	Conclusion	68		Conclusion: Vision of Clinical Research	
	Acknowledgment	68		in the 21st Century	85
	References	68		Glossary	86
	Recommended Resources	69		List of Acronyms and Abbreviations	86
				References	87

6.	Health-Care Technology Assessment (HTA)		Assessing Medical Interventions: Outcomes, Effectiveness, and Cost-Effectiveness	113
	Uwe E. Reinhardt		Assessing Medical Interventions  Medical Decision-Making	114 117
	2	0.0	Quality Medical Care	123
	Summary	92	Variations in Care	123
	Introduction	92	Medical Errors and Safety	127
	The Evaluation of New Medical Technology:		Disparities and Inequities of Care	130
	The Producer's Perspective	93	Quality Management and Improvement	131
	Private, Investor-Owned Producers of New	0.0	Conclusions	132
	Medical Technology	93	References	132
	Public Producers of New Technology	95	References	132
	The Evaluation of New Medical Technology:	0.5		
	The End User's Perspective	95	Section II	
	The Ethical Precepts Driving Markets	96		
	The Implications of the Market Approach for	06	Approaches	
	the Producers of New Medical Technology	96		
	The Evaluation of New Medical Technology:	97	8. Measurement of Biological Materials	
	Society's Perspective The General Framework for Technology	97	Mark D. Kellogg	
	Assessment in Health Care	97		
	Defining Net Incremental Benefits	98	Introduction	138
	Whose Costs and Benefits?	99	Immunoassays and Immunochemistry	138
	The Issue of Discounting Costs and Benefits	99	Background	138
	Should Benefits Be Age Adjusted?	100	Basic Principles	138
	Cost—Benefit, Cost-Effectiveness, and Cost—	100	Enzyme Immunoassays	139
	Utility Analysis	100	Other Types of Immunoassays	140
	Cost—Benefit Analysis	100	Characterization of Immunoassay Performance	142
	Cost-Effectiveness Analysis	102	Mass Spectrometry and Chromatography	142
	Cost—Utility Analysis: Quality-Adjusted Life	102	Background	142
	Years and Disability-Adjusted Life Years Lost	102	Basic Principles	142
	Can One Ever Avoid Putting Monetary Values	102	Gas Chromatography	143
	on Health Benefits?	106	Liquid Chromatography	144
	Comparing Alternative Treatments	106	Mass Spectrometry	145
	Cost-Effectiveness Analysis and Cost-Utility		Mass Analyzers and Modes of Analysis	146
	Analysis and National Health Policy	107	Mass Spectrometry and Clinical Research	148
	Unresolved Controversies on Economic		Genomics	148
	Valuations in Health Care	108	Background	148
	Methodological Issues	108	Basic Principles and Methodological	1 4 0
	Objections on Ethical Grounds	108	Considerations	148
	Objection on Commercial Grounds	109	Summary and Applications to Clinical and	1.40
	References	109	Translational Research	149
			Proteomics, Lipidomics, Metabolomics, and Multiomics	1.40
7.	Health Services Research: Translating		Background	149 149
	Discovery and Research Into Practice		Basic Principles and Methodological	145
	and Policy		Considerations	151
	,		Applications of -Omic Analysis	151
	J. Sanford Schwartz		Summary and Applications to Clinical and	132
	Introduction	112	Translational Research	153
	What Is Health Services Research and What		Conclusion	153
	Are Its Goals?	112	References	153
		0.00	nord offices	100

9.	Imaging Tools in Clinical Research: Focus on Imaging Technologies			Clinical Applications of Nanotechnology for Research	193
	Ruth M. Dunne, Ailbhe C. O'Neill and Clare M. Tempany			Nanoparticle-Targeted Drug Delivery Nanoparticles for Analytical Techniques Conclusion and Future Directions in	193 199
	Introduction	158		Nanomedicine	203
	Imaging Technologies	158		References	203
	Overview	158			
	Computed Tomography	158	12.	The Use of Questionnaires and	
	Magnetic Resonance Imaging	162		Surveys	
	Ultrasound	167		Marcia A. Testa and Donald C. Simonson	
	Nuclear Medicine	170		Marcia A. Testa and Donaid C. Simonson	
	Optical Imaging	173		Introduction	207
	Conclusion	176		The Practice of Questionnaire and Survey	
	References	176		Measurement	208
				The Emergence of Questionnaire and	
10.	Imaging Tools in Human Research:			Survey Measurement in Clinical	
	Focus on Image-Guided			Investigation	208
	Intervention			Items, Scales, Questionnaires, and	
	Buth M. Donne Allele C. O'Alell			Instruments	210
	Ruth M. Dunne, Ailbhe C. O'Neill			The Role of Psychometrics	211
	and Clare M. Tempany			Questionnaires Used to Assess Patient-	
	Introduction	182		Reported Outcomes	211
	Image-Guided Biopsy	182		Choosing the Appropriate Questionnaire	215
	Breast	182		The Different Types of Questionnaires	217
	Lung	182		Types of Health Outcomes Assessed Using	
	Prostate	183		Questionnaires	218
	Image-Guided Therapy	184		Evaluating Questionnaires and Survey	
	Ablation	184		Instruments	218
	Focused Ultrasound	185		Reliability, Validity, Sensitivity, and	
	Targeted Drug Delivery	187		Responsiveness	220
	Hybrid Operating Room	187		Item Response Theory, Dynamic	
	Treatment Planning in Radiation Oncology—			Questionnaires, and Computer	222
	The Role of the Radiologist	188		Adaptive Testing Statistical and Analysis Considerations	222
	Conclusion	188		Analysis and Interpretation of	223
	References	188		Multiple, Hierarchical, and Correlated	
44				Scales	223
11.	Nanotechnology in Clinical and			Interpreting a Minimal Clinically Important	223
	Translational Research			Difference	223
	James R. Baker Jr., Brent B. Ward and			Summary and Conclusions	224
	Thommey P. Thomas			Glossary	224
				List of Acronyms and Abbreviations	225
	Introduction and Historical Perspective	191		References	225
	History of Nanotechnology in Medicine	191			
	Rationale for Nanotechnology in Medicine	100	13.	Information Technology	
	and Research	192		01	
	Nanotechnology in Basic Research			Shawn N. Murphy, Henry C. Chueh and	
	Applications Supporting Clinical Translation	102		Christopher D. Herrick	
	Knockout of Specific Biomarkers and Genes	192 192		Introduction	228
	Structural Analysis of Proteins	193		Clinical Data Repositories	228
	Artificial Substrates to Examine Cellular	193		Harnessing the Clinical Enterprise as a Data	
	Functions	193		Source	228

	Clinical Data Repositories: A Problematic			<b>Baseline Comparisons and Primary Outcome</b>	
	Data Source	228		Analysis	249
	The Expanding Use of Preresearch Clinical			Generalized Linear Models	251
	Registries	228		Linear Regression Model for the Continuous	
	Design for Research Data Warehouses	229		Data	251
	Metadata	230		Logistic Regression Model for the Binary	
	Aggregating Data	232		Data	252
	Work Processes	233		Survival Analysis for the Censored Data	253
	Considerations for Warehousing Genomic			Model Building	255
	Data	233		Distribution of the Explanatory Variables	256
	Research Data Warehouse Versus	233		Confounding	256
	Population Management Databases	234		Interaction Effects	256
	Information Technology Support of	231		Nonlinearity	256
	Participant Recruitment	235		Model Selection	256
	Strategies for Participant Recruitment	235		Collinearity	256
	Reaching Only Interested Participants	235		Multiple Comparisons	257
	Identifying Only Eligible Participants	235		Missing Data	257
	Principles of Data Collection	236		Linear Mixed-Effects Models (Clustered	237
	Automation and the Human Element	236		or Longitudinal Studies)	258
		230		Conclusion	259
	Data Validity: Capturing Data With Consistent Metadata	226		References	
		236		References	260
	Continuous Quality Assurance	236	15	Cood Clinical Dreatice and Cood	
	"Stand-alone" Electronic Data Capture	236	15.	Good Clinical Practice and Good	
	Integration With Clinical Documentation	236		Laboratory Practice	
	Problems With Integrated Models	237		Nathalie K. Zgheib, Stephanie L. Tomasic and	
	Data Standards	238		Robert A. Branch	
	Use of Web Standards	238			
	Content Standards	239		Overview	262
	Clinical Trial Management Systems	239		Good Clinical Practice	262
	Publicly Available Databases	239		Introduction	262
	Biomedical Literature	240		Definition	262
	Clinical Trials and Research	240		Rules and Regulations	262
	Evidence-Based Medicine	240		Clinical Practice and Research	263
	The Growing Impact of Big Data and the			Key Participants in Clinical Research	265
	Cloud	240		Documentation and Record Keeping	270
	Conclusion	241		Data Management and Presentation	271
	References	241		Monitoring and Compliance	27
				Conclusion	272
14.	Principles of Biostatistics			Good Laboratory Practice	272
	Kush Kapur			Introduction	272
	кизп кариг			Definition and Scope	272
	Introduction	243		Organization and Personnel	273
	Types of Data	244		Management of the Testing Facility	273
	Descriptive Statistics	245		Quality Assurance	274
	Central Limit Theorem	246		Test, Reference, and Control Articles	275
	A Cautionary Note on the Application of			Protocol for and Conduct of a Nonclinical	
	Central Limit Theorem	247		Laboratory Study	275
	Testing and Summarizing Relationship			Reporting of Nonclinical Laboratory Study	
	Between Two Variables	248		Results	276
	p-Value and Confidence Intervals	248		Record Keeping	276
	Type I and II Error Rates	249		1 0	

	Disqualification of Laboratory Facility Resources	276	17.	Epidemiologic and Population Genetic Studies	
	Conclusion	277		Angela J. Rogers and Scott T. Weiss	
	Glossary	277			
	List of Acronyms and Abbreviations	277		Introduction	314
	References	277		Design Issues in Genetic Association Studies Population Issues: Defining a Phenotype and	315
Sec	ction III			Selecting Epidemiologic Study Design  Epidemiologic Study Design	315 316
	man Genetics			Case—Control Studies	316
Hu	illian deficties			Cohort or Population Studies	316
16.	Introduction to Human Genetics			Family-Based Studies	317
	Bruce R. Korf			Comparison of Family-Based Versus Case— Control Studies	317
	Introduction	282		Genetic Study Design: Genome-Wide	
	Basic Molecular Genetics	282		Association Study Versus Hypothesis-	
	DNA Structure	282		Driven (Candidate Gene) Approaches	317
	DNA Replication	283		Hypothesis-Free Testing: Genome-Wide	
	Transcription	283		Association Study	318
	Translation	285		Candidate Gene or Region-Based Testing,	
	Chromosome Structure and Function	286		With a Focus on SNP Selection	318
	Mitosis and Meiosis	287		Interpreting Results of Genetic Association	0.1.0
	Gametogenesis	288		Studies	319
	Patterns of Genetic Transmission	288		Genotype Quality Control	320
	Single Gene Inheritance (Mendelian	41		Correction for Multiple Comparisons	321
	Inheritance)	289		Population Stratification	322
	Non-Mendelian Inheritance	291		Power	323
	Multifactorial Inheritance (Polygenic			Future Directions	324
	Inheritance)	295		Emerging Biologic Targets	324
	Cytogenetics and Chromosomal			Integrative Statistical Approaches	325
	Disorders	295		From Association to Functional Variant	325
	Methods of Chromosomal Analysis	295		Conclusion	325
	Chromosomal Abnormalities	296		References	325
	The Human Genome	298	10	Dhawes as as at less of Dwg	
	Structure and Organization of the		10.	Pharmacogenetics of Drug	
	Genome	298		Metabolism	
	Genetic Variation	299		Zeruesenay Desta and David A. Flockhart	
	Mutation and Polymorphism	299			207
	Genotype-Phenotype Correlations	302		Introduction	327
	Medical Applications	303		Pharmacogenetics of Drug Metabolism:	220
	Molecular Diagnostic Testing	303		Historical Aspects	328
	Therapy of Genetic Disease	306		Genetic Polymorphisms of Individual	220
	Genetic Counseling	308		Drug-Metabolizing Genes	329
	Phenotyping and Clinical Research	309		CYP1A2	329
	Genotype-Environment Interaction	309		CYP2B6	330
	Phenotypic Complexity	310		CYP2C8	332
	Approaches to Gene Discovery	310		CYP2C9	333
	Conclusion	311		CYP2C19	335
	References	311		CYP2D6	336
	Bibliography	311		CYP3A5	338

	N-acetyitransierase 2	340		Transporters and Drug Absorption,	
	Thiopurine Methyltransferase	340		Distribution, and Excretion	366
	UDP-Glucuronosyltransferase	341		Intestinal Transporters	368
	Butyrylcholinesterase	342		Hepatic Transporters	368
	Conclusions	343		Renal Transporters	369
	References	343		Drug-Metabolizing Enzymes	370
				CYP2C9/CYP2C19	371
19.	Statistical Techniques for Genetic			CYP2D6	371
	Analysis			CYP3A4/CYP3A5	372
	,			Drug-Drug Interactions	372
	Jessica Lasky-Su			Clinically Important Drug-Metabolism-	
	Introduction	348		Associated Interactions	372
	Genetic Determination of Complex Disease	348		Transporters and Drug Interactions	373
	Twin Studies	348		Induction and Regulation of Drug-	
	Family Studies	348		Metabolizing Enzymes and Transporters	373
	Adoption Studies	348		Principles of Pharmacokinetics	375
	Genetic Linkage Studies	349		Introduction to Pharmacokinetics	375
	Common Genetic Study Designs and	3.5		Pharmacokinetic Concepts	375
	Statistical Tests	349		Dose Selection	381
	Case—Control Studies	350		Intermittent Dose Administration	382
	Population-Based Studies	350		Conclusion	383
	Family-Based Association Studies	351		References	383
	Genomewide Association Studies	351			000
	Population Stratification Adjustment	352	21.	Adverse Drug Events	
	Multiple Testing Adjustment	352			
	Next-Generation Sequencing	354		Dan M. Roden	
	Rare Genetic Variant Analysis	354		The Multifactorial Nature of Adverse Drug	
	Metaanalysis Techniques	355		Events	389
	Gene-By-Environment Analysis	355		Types of Adverse Drug Events	390
	Multivariant Approaches	356		System Errors	390
	Multiple Regression Analyses	356		Linking Events to Drug Administration—the	330
	Discrimination Methods	356		"Easy" Examples	390
	Network Medicine	356		Linking Events to Drug Administration—the	330
	Basic Network Theory	356		"Hard" Examples	390
	Correlation Coexpression Networks	357		Adverse Drug Events Due to Aberrant Drug	330
	Pathway Analyses	357		Disposition (Variable Pharmacokinetics)	391
	Integrative Omics	358		Adverse Drug Events Not Due to Elevated	331
	Phenotypic Limitations	359		Drug or Metabolite Concentrations	393
	Computer Programs	359		Genetics to Genomics	394
	Summary and Conclusions	359		References	394
	Glossary	359		References	334
	List of Acronyms and Abbreviations	360			
	References	360	500	stion \/	
	References	300		ction V	
			Soc	cietal Context of Human Researd	ch
Sec	ction IV		22	Translating Calanas to the Desiries	
	man Pharmacology		22.	Translating Science to the Bedside:	
110	man marmacology			The Innovation Pipeline	
20.	Introduction to Clinical			Seema Basu	
	Pharmacology			Realities of the Marketplace	400
	Rommel G. Tirona and Richard B. Kim			What Are the Phases Involved in Taking	
				Ideas/Discoveries to the Patient's Bedside?	
	Introduction: Mechanisms of Drug	0.55		What Are the Critical Issues to Consider	
	Disposition and Interactions	366		at Each Phase?	402

	How Does This Differ for Various Types of Technology? What Are the Market Pres- sures for Devices, Software, Diagnostics,			Translating Science to the Bedside Cores in Academic Health Centers How the Innovation Office Help Partners	419
	Therapeutics, and Research Tools?	402		HealthCare Researchers	419
	What Funding Sources Support			Summary	421
	Development and Creation of Products			Statutes and Federal Regulations	421
	and Services?	403		Cases	421
	What Are the Roles of Government,			Endnotes	421
	Philanthropy, and Industry?	403		References	421
	Types of Relationship: Sponsored Research,				
	Grants, Codevelopment, and Gifts	403	23.	Regulatory Environment	
	What Resources Are Available at Academic				
	Health-Care Systems to Help Translational			Christine Nguyen, Audrey Gassman and	
	Researchers Bring Products and			Hylton V. Joffe	
	Technologies to Market for Patient			Introduction	423
	Benefit?	404		The US Food and Drug Administration	424
lo	deas and Innovations	404		Overview	424
	What Is Intellectual Property?	404		Organization	424
	Why Are Patents and Copyrights Important?	406		Legal Authority	425
V	Vorking With Industry	407		Nonclinical Testing	426
	The Academic Health-Care System as			The Investigational New Drug Application	427
	a "Living Laboratory"	407		The Marketing Application	433
	Common Challenges	409		Expanded Regulatory Authority on	
E	ntrepreneurship	410		Postmarket Drug Safety	435
	Market Opportunity: What Problem Am I			Other Regulatory Agencies	436
	Solving?	410		Conclusions	436
	Technology: What Is the Status of the Core			Glossary	436
	Technology?	410		List of Acronyms and Abbreviations	437
	Financial: How Much Money Will It Take			Acknowledgments	437
	to Get This Idea to Market? Where Will It			References	438
	Come From?	411			
	Management: How Do I Think About the		24.	Ethical Issues in Translational	
	Right People, Skills, and Change of			Research and Clinical Investigation	
	Control?	412			
	Legal and Regulatory Affairs: What Kind of			Greg Koski	
	Help Do Entrepreneurs Need at the Early			Introduction	442
	Stages?	412		The Ethical Dimension of Scientific Inquiry	442
(	Clinical Evaluation of Innovative Products	413		Responsibility in Science and Society	443
	How Does Clinical Evaluation Differ From			Responsibilities of Scientists	443
	Earlier Stages of Innovation?	413		Societal Responsibilities	443
	How Is the Complex Relationship Between			Ethics and Translational Research	443
	Safety and Innovation Managed?	413		Guiding Principles for the Responsible	
	What Are the Role and Responsibilities of			Translational Investigator	445
	the Principal Investigator?	413		Beyond Ethics: Regulations, Compliance, and	ł
	What Are the Roles and Responsibilities of			Professionalism in Translational Research	446
	the Sponsor?	414		Justice, Beneficence, and Respect for Persons:	:
	What Is the Role and Responsibility of the			From Principles to Practice	447
	Food and Drug Administration?	414		Research Risks, Harm, and Injury	447
	How Do Academic Health Centers Support			Benefits	448
	and Guide These Roles?	415		Special Populations	448
	Why Is a Clinical Trial Agreement Needed?	415		Issues in Collection of DNA and Other	
	How Do I Get Started?	416		Biospecimens for Research	448
(	Conflicts of Interest	416		Regulation of Research and Protection of	
	What Are Conflicts of Interest?	416		Subjects	449
	Required Components of Conflict of Interest			Research and Regulations in the United	
	Policies	417		States	449

	Nongovernmental Agencies and Associations Public Perception of Clinical Research	452		Conclusion Acknowledgment	474 475
	Protection of Human Subjects Review and Oversight Institutional Review Boards and Ethics	452 452		References	475
	Committees	453	Sec	ction VI	
	Data and Safety Monitoring Boards,			search in Special Populations	
	Medical Monitors, and Subject Advocates	452			
	Medicolegal Framework, Liability,	453	26.	Research in Special Populations:	
	and Risk Management	453		Acute Illnesses; Critical Care; and	
	Individuals and the Clinical Research	433		Surgical Patients	
	Process	454			
	Motivation and Expectations of the	TJT		Todd W. Rice and Gordon R. Bernard	
	Volunteer Subject	454		Introduction	482
	Motivation of the Scientist and Conflicts	434		Trial Design	482
	of Interest	455		Type of Study	482
	Professionalism in Clinical Research	455		Selecting a Control Group	483
	References	456		Placebo-Controlled Studies in Surgical	
				Patients or Nonsurgical Invasive	
25.	Clinical Research in the Public			Procedures	484
	Eye			Usual Care in Critically III Patients	485
	•			Studies Comparing Usual Care Components	485
	Mary Woolley			Protocolized Nonstudy Treatment	486
	Introduction	457		Informed Consent	488
	The Cultural Context of Research	459		Surrogate Informed Consent	489
	The Lens of Health and Health Care	459		Waiver of Consent in Emergency Research	490
	Shifting Power to the Patient	459		Outcomes	490
	Public Input and National Institutes of			Associated Versus Attributable Outcomes	490
	Health	460		Endpoints	491
	Public Perception of Research	460		Adverse Events	495
	Privacy Issues	462		Conclusion	496
	The Internet and an Empowered Public	465		References	496
	Continuing Challenges	466	~=	D 11.11.5	
	Electronic Media Technology Changes		27.	Research in the Emergency Care	
	Everything	466		Environment	
	Research Information and the News			James Quinn and Daniel J. Pallin	
	Media: Scientists' Role	467			
	The Celebrity Factor	468		Introduction	501
	Unrealistic Expectations?	468		The Environment and Unique Challenges of	
	Science and Politics	469		Emergency Care Research	501
	The Small Voice of Science: Stepping			Examples of Early Success	502
	Up to Strengthen It	469		Building an Emergency Care Research Site	503
	The Role and Influence of the White			Funding of Infrastructure in the Emergency	
	House	470		Care Environment	504
	How Congress Influences Medical			The Role of Industry	505
	Research	471		Implementation of Emergency Care Research	506
	Making the Case for Research to			Recruitment	506
	Congress	472		Trial Design Considerations	508
	The Role and Influence of Patient Advocacy			Retention of Patients and Strategies to	E10
	Organizations	472		Enhance Follow-Up Conclusion	510
	The Role and Influence of Philanthropy	473		References	510 511
	Public-Private Collaboration	473		Note: Circos	211

28.	Psychiatric Disorders			Conclusions and Recommendations References	550 550
	Alan F. Schatzberg				330
	Introduction	515	30.	Clinical Research in Neurology	
	Diagnostic Issues	515		Keren Regev and Howard L. Weiner	
	Adults Special Age- and Gender-Based Populations	515 516		Introduction	555
	Types of Studies	517		Features Unique to Neurologic Diseases	556
	Epidemiological	517		The Challenges	556
	Observational	517		Disease Examples	558
	Mechanism and Physiology	517		Multiple Sclerosis	558
	Disease Mechanisms	518		Alzheimer Disease	561
	Treatment	518		Amyotrophic Lateral Sclerosis	564
	Translational Research	518		Glioma	566
	Tools	519		Acute Ischemic Stroke	567
	Behavioral Measures	519		Conclusion	568
	Biological Measures	519		References	568
	Imaging	523	21	December in Dedictries	
	Genetics	523	31.	Research in Pediatrics	
	Statistical and Design Issues Power	524 524		Lisa Bomgaars, Stacey Berg and Ann R. Stark	
	Predictors and Moderators	524		Introduction	573
	Special Issues	525		What Is Different About Pediatric Research?	574
	Treatment Studies	525		Developmental Physiology	574
	Behavioral Research in Medical Disorders	527		Limitations Related to Body Size	576
	A Practical Schematic Approach	528		Orphan (Rare) Diseases	576
	Summary	530		Population Available for Study Is Smaller in	
	References	530		Children Than in Adults	576
20	Describe in Chasial Danulations			Small Numbers Mean Multicenter Trials Are	576
29.	Research in Special Populations:			Usually Required  Lack of Pediatric Guidelines for Most Drugs	577
	Geriatrics			Need for Very Long-Term Follow-up to	3//
	Stephanie Studenski and Luigi Ferrucci			Determine Outcomes	578
	Introduction	533		Pediatric Conditions as Focus of Inquiry	579
	What Is Different About Aging Research?	534		Prematurity	579
	Disease and Aging	534		Childhood Cancers That Do Not Occur in	
	A Conceptual Model to Account for the			Adults	580
	Causes and Consequences of Altered			Regulatory and Ethical Environment for	
	System Structure and Function With Aging	534		Pediatric Research	580
	The Effect of Aging on Practical Aspects of			Risk Categories	581
	Clinical Research	537		Assent/Permission Procedures	581
	How an Aging Perspective Affects Research			Conclusion	582
	Topics and Approaches	538		Statutes and Regulations	582
	Overview	538		Cases	583
	Translational Research	538		References	583
	Clinical Trials	539	33	Cancer as a Paradigm for	
	Population-Based Research The Effect of Aging on the Pragmatics of	542	32.	Translational and Clinical	
	The Effect of Aging on the Pragmatics of Research	543		Biomedical Research	
	Overview	543		Diomedical Research	
	Samples	545		César Serrano and George D. Demetri	
	Measures	546		Introduction	588
	Important Measures for Aging Populations	547		Cancer: From the Edwin Smith Papyrus	
	Interventions	547		to the Molecular Genetic Era	588
	Analysis	547		Defining Subgroups in Cancer	589

	Using a Mentor Effectively The Mentorship Committee Career Development Resources	646 646 647	Section IX Research in Academia	
	Funding for Training Clinical and Translational Investigators Further Reading	647 647	38. Industry-Sponsored Clinical Research in Academia	
26	A Stanuisa Annuach to a Canaan		Italo Biaggioni	
36.	A Stepwise Approach to a Career		Introduction 6	71
	in Translational Research		The Public Perspective 6	72
	William F. Crowley Jr.		The Academic Health Center Perspective 6	72
		649	The Industry Perspective 6	73
	Definitional Issues	650	The investigators i crop-serve	74
	Historical Perspective	651	Matching Industry Needs and Academic	
	Step 1: The Starting Point	031		574
	Step 2: The Need for Normative Data and	652	Academic Clinical Trials Centers As a	
	Control Populations	032		575
	Step 3: Engaging Relevant Basic Researchers and Their Technologies	652	0	575
	Step 4: Identifying Tractable Problems	653	Information Technology Solutions to Improve	
	Step 5: Identifying Appropriate Mentors	033		576
	Across a Career	653		576
	Step 6: Obtaining Successful Independent	033		577
	Funding	654	References	577
	Step 7: The Perils of Senior Leadership	654		
	Summary	655	39. Governmental Support of Research	
	References	655	Sten H. Vermund and Salim Abdool Karim	
27	Dharinian Canages in the		Introduction	680
3/.	Physician Careers in the		Overview	680
	Pharmaceutical Industry		United States Government Scientific	
	Ronald L. Krall		Programs	581
		650	The National Institutes of Health	584
	Introduction	658	The Centers for Disease Control and	
	Medical-Scientific Positions in the	(50		689
	Pharmaceutical Industry	659	Scientific Programs in Europe, Canada, and	
	Experimental or Translational Medicine	659		690
	Clinical Pharmacology	660 660	1	690
	Clinical Research Physician	661	, tational interaction	692
	Medicine Safety and Pharmacovigilance Medical Affairs	663	Scientific Programs in Asia, Africa and South/	
	Regulatory Affairs/Regulatory Science	663		693
	Pharmacoepidemiology and Health	003		693
	Outcomes Research	664	Balancing the Needs of Intramural and	
	Project Leadership	664		696
	Management	665	Supporting Capacity Building Through Grants	
	Medical Officer: Decisions That Require	003		697
	Medical Input	665	New Initiatives to Recognize and Support	
	A Pharmaceutical Career	666		697
	Summary	666	Current Support for Clinical and Translational	
	References	666		697
	References	500	Conclusion	699