

TABLE OF CONTENTS

Acknowledgements	iii
Preface	v
About the Authors	xi
Copyright Acknowledgements	xv

PART I: BACKGROUND AND REGULATORY CONTEXT

Chapter 1 HISTORICAL ANTECEDENTS	3
§ 1.01 Early Examples of Human Experimentation	4
[A] Ancient Activity	4
[B] Approaches through the Mid-Twentieth Century	6
[1] European Medical Education and Practice	6
[2] Statistics and Research	7
[3] The Revolution in American Medical Education	8
[4] Early Experiments on Venereal Disease	9
[5] Rabies and Yellow Fever	12
§ 1.02 American Judicial Reaction to Experimentation	14
§ 1.03 Nazi Germany and the Nuremberg Code	16
[A] Introduction	16
[B] The Indictment	17
[C] Opening Argument	19
[D] The Trial	22
[1] Testimonial Evidence (Excerpts)	22
[2] Documentary Evidence (Excerpts)	24
[E] Defendants' Final Statements	25
[F] Excerpts from the Judgment of the Tribunal, including the Nuremberg Code	26
§ 1.04 Medical Research in the United States from 1900 to the Early 1970s	31
[A] Pre- and Post- World War I Research Activities	31
[B] Funding of U.S. Research through World War II	32
[C] The Developing Public Role In Research	34
[D] The Need to Conduct Appropriate Research: Thalidomide and DES	35
[E] The Beecher Article (1966)	37
[F] Jewish Chronic Disease Hospital (1963) and Willowbrook (1956-1971)	39
[G] Tuskegee (1932-1972)	41
[H] Radiation Experiments (1944-1974)	44

[I] Behavioral and Social Science Research: The Milgram Experiments	48
Chapter 2 THE CHANGING FACE OF RESEARCH: NEW REGULATIONS, NEW PLAYERS, NEW PLACES, NEW AGENDAS	51
§ 2.01 Governmental Oversight of Research	51
[A] Federal Oversight: 1960s to 1990s	51
[B] New Directions in Federal Regulation: 1996-2003	57
§ 2.02 Biomedical Advances, New Funding, New Places, New Players	61
[A] Research Successes of the 1980s and 1990s	61
[B] How Much Do We Spend on Research?	63
[C] The Changing Role of Academic Health Centers in Research	65
[1] Bayh-Dole	67
[2] Current Clinical Research Funding Streams	69
[D] Federal Sources of Research Funding	73
[1] National Institutes of Health	73
[2] Other DHHS Departments	74
[3] Other Federal Agencies	75
[E] Private Industry Funding of Research	76
[1] Pharmaceutical Companies	76
[2] Biotech Companies	76
§ 2.03 The Movement of Research from Academic Health Centers To Private Physicians' Offices and the Rise of Contract Research Organizations	77
§ 2.04 Developing New Research Agendas	86
[A] Setting NIH Priorities	87
[B] The Role of Advocacy	95
[1] Legislative Advocacy	96
[2] Advocacy Regarding the Manner in Which Research Is Conducted	100
Chapter 3 THE FEDERAL AND STATE REGULATORY STRUCTURE	105
§ 3.01 Overview of the Legal Structure	105
§ 3.02 Department of Health and Human Service Regulations	106
[A] The Common Rule	106
[1] Scope of Coverage	107
[2] Definition of Research	107

TABLE OF CONTENTS

xxvii

[a] What Is a Research Protocol?	108
[b] Research versus Clinical Innovation	109
[c] Research versus Quality Improvement	115
[d] Research versus Public Health Initiatives	119
[3] Definition of Human Subject	121
[4] Exempt Studies	123
[B] Additional DHHS Regulations Governing Vulnerable Populations	125
[C] The DHHS Office for Human Research Protections	136
§ 3.03 Food and Drug Administration Regulations	142
[A] Human Subject Protections	143
[B] The Drug Approval Process	144
[C] The Device Approval Process	157
[D] FDA Office for Good Clinical Practice	160
§ 3.04 Research Not Covered by Federal Regulations	161
§ 3.05 State Laws	163
Chapter 4 INSTITUTIONAL REVIEW BOARDS	169
§ 4.01 Purpose and Duties	169
§ 4.02 Composition	175
§ 4.03 Process of IRB Review	179
[A] Full Review	179
[B] Expedited Review	195
§ 4.04 Proprietary and Independent IRBs	197
§ 4.05 Accreditation	202
Chapter 5 CONFLICTS OF INTEREST	207
§ 5.01 Investigator Conflicts	207
§ 5.02 Institutional Conflicts	232
§ 5.03 IRB Conflicts	237
§ 5.04 Disclosing Conflicts of Interest to Subjects	239

PART II:**REVIEWING RESEARCH PROPOSALS: GENERAL CONSIDERATIONS**

Chapter 6 RISK-BENEFIT ASSESSMENT	245
§ 6.01 The Role of Risk-Benefit Assessment in Research Oversight	245
§ 6.02 Identifying Risks	247
[A] The Concept of Risk	247
[B] Risks to Research Subjects	250
[1] Introduction: A Typology of Research Risks	250

[2] Distinguishing the Risks of Research from the Risks of Interventions That Would Otherwise Be Performed	254
[3] The Concept of Clinical Equipoise	256
[4] Clinical Equipoise and the Use of Placebo Controls . .	262
[5] Washouts and Challenge Studies	271
[C] Risks to Others	279
[D] “Minimal Risk” Research under the Federal Regulations	280
§ 6.03 Identifying Benefits	282
[A] Potential Benefits to Research Subjects	282
[B] The Production of Knowledge as a Benefit of Research	286
§ 6.04 Balancing Risks and Benefits	289
§ 6.05 Minimizing Risks	295
Chapter 7 INFORMED CONSENT	297
§ 7.01 From Consent to Medical Care to Consent to Research	298
[A] Informed Consent to Medical Care	298
[1] Case Law	298
[2] Medical Practice Guidelines	303
[B] Informed Consent to Innovative Treatment	304
[C] Informed Consent to Research	307
§ 7.02 Federal Regulations Governing Informed Consent to Research	312
[A] General Requirements	312
[B] Waivers and Alterations of the Usual Requirements	313
[1] General Waivers	313
[2] Waivers in Emergency Research	318
§ 7.03 Implementing the Federal Regulations	327
[A] The Consent Form	327
[B] Informed Consent as a Process	344
[C] An Informed Consent Script	351
§ 7.04 Deficiencies in the Informed Consent Process	355
[A] The Therapeutic Misconception	355
[B] Failure to Convey Information	363
[C] Cultural and Gender-Based Barriers to Informed Consent	366

TABLE OF CONTENTS

xxix

Chapter 8 RECRUITING AND PAYING SUBJECTS	371
§ 8.01 Recruiting Subjects	371
[A] Overview of the Issues	371
[B] Agency and Institutional Guidance	378
[1] FDA	378
[2] OHRP	381
[C] Institutional Policies	384
[D] Recruiting Normal Healthy Subjects	386
[E] Soliciting Students or Employees of Researchers	391
§ 8.02 Paying Subjects	395
[A] Agency Guidance	395
[1] FDA	395
[2] OHRP	397
[B] Determining an Appropriate Level of Payment	402
[C] Structuring Payments	405
Chapter 9 RESEARCH AND JUSTICE: PROMOTING THE INCLUSION OF WOMEN AND RACIAL MINORITIES	409
§ 9.01 The Concept of Justice in Research with Human Subjects	409
§ 9.02 Justice and Women	415
[A] Federal Policy Before 1993	415
[B] Revisions in Government Policies	426
[1] FDA	426
[2] NIH	430
[3] Further FDA Revisions	432
§ 9.03 Justice and Racial Minorities	433
Chapter 10 CONFIDENTIALITY	443
§ 10.01 Overview of Medical Confidentiality	443
[A] Confidentiality as an Ethical Principle	443
[B] Legal Sources of Medical Confidentiality	446
[1] State Laws	446
[2] Federal Law	447
§ 10.02 Confidentiality Issues in Research	448
[A] Maintaining the Confidentiality of Research Data	448
[1] General Issues	448
[2] Certificates of Confidentiality	452
[B] Overseeing the Use and Disclosure of Medical Records	456
[1] Human Subject Protection Regulations	456
[2] HIPAA Regulations	459

Chapter 11 MONITORING OF ONGOING RESEARCH . . .	465
§ 11.01 Continuing Review	465
§ 11.02 Adverse Event Reporting	470
§ 11.03 Data and Safety Monitoring Boards	475
Chapter 12 COMPENSATION FOR RESEARCH INJURIES	487
§ 12.01 Ethical Considerations	487
§ 12.02 The Regulatory Framework	495
§ 12.03 Tort Liability	495
[A] The Emerging Role of Tort Litigation in Human Subject Research	496
[B] Defining Researchers' Duties to Subjects	502
[C] Additional Issues in Informed Consent Cases	510
§ 12.04 No-Fault Compensation	519
[A] Voluntary No-Fault Compensation Schemes	520
[B] Proposals for Comprehensive No-Fault Compensation Systems	522

PART III:

REVIEWING RESEARCH PROPOSALS: SPECIAL SITUATIONS

Chapter 13 CHILDREN	527
§ 13.01 Research with Children: Past and Present	527
§ 13.02 The Regulatory Framework	533
[A] Decision-Making Authority of Parents and Children	533
[1] Parental Authority: Permission and Refusal	533
[2] Soliciting a Minor's Assent	538
[3] Allocating Decision-Making Authority in Research with Adolescents	541
[B] Categories of Permissible Risk	544
[1] General Principles	544
[2] Applying the Standards: The Fenfluramine Studies	551
[C] DHHS Review of Research Not Otherwise Approvable	554
[1] Cystic Fibrosis in Neonates	555
[2] Smallpox Vaccination in Young Children	562
§ 13.03 Pediatric Research in the Courts: The <i>Kennedy Krieger</i> Case	567

TABLE OF CONTENTS

xxxii

Chapter 14 ADULTS WHO LACK DECISION- MAKING CAPACITY	585
§ 14.01 The Appropriateness of Conducting Research with Adults Who Lack Decision-Making Capacity	586
§ 14.02 Determining Whether Subjects Lack Decision- Making Capacity	591
[A] Defining Decision-Making Capacity	591
[B] Assessing Decision-Making Capacity	598
§ 14.03 Informed Consent	601
[A] Surrogate Decision Making	601
[B] Research Living Wills	609
[C] Subject Assent and Refusal	612
§ 14.04 Limitations on Permissible Risks	613
§ 14.05 Constitutional Considerations	621
 Chapter 15 PRISONERS	 629
§ 15.01 General Considerations	629
[A] The U.S. Prison Population	629
[B] History of Medical Research in Prisons	635
§ 15.02 Federal Regulation of Prison Research	642
[A] Overview of Subpart C	642
[B] OHRP Questions to NHRPAC on the Interpretation of Subpart C	645
§ 15.03 The Shift From Protection to Access	647
§ 15.04 Research with Incarcerated Children	650
 Chapter 16 FETUSES AND EMBRYOS	 655
§ 16.01 Fetal Research	655
[A] Research on Fetuses in Utero	655
[B] Research on Tissue from Aborted Fetuses	657
[1] Federal Law	657
[2] State Law	658
§ 16.02 Embryo and Embryonic Stem Cell Research	661
[A] Perspectives on Embryo and Embryonic Stem Cell Research	662
[B] Federal Law and Policy	672
[1] General Federal Policy on Embryo Research	672
[2] Application of Federal Embryo Research Policies to Research on Embryonic Stem Cells	676
[C] State Law and Policy	681
[D] Consent to Embryo and Embryonic Stem Cell Research	683
§ 16.03 Cloning	686

[A] What Is Cloning?	686
[B] Perspectives on Cloning	688
[C] Federal Law	693
[D] State Law	695
Chapter 17 GENETICS RESEARCH	697
§ 17.01 Research Designed to Learn About the Genome	697
[A] What the Genome Can Tell Us: The Power and Perils of Genetic Information	698
[B] Sources of Biological Materials for Genetics Research . . .	701
[C] Necessity of IRB Review of Genetic Testing Research . . .	703
[1] Definition of “Human Subject”	703
[2] Exempt Research	706
[D] Risk Assessment	707
[1] Risks to Subjects	707
[2] Risks to Others	709
[3] Risk Assessment and Eligibility for Expedited Review	714
[E] Informed Consent	715
[1] Research Involving the Collection of New Tissue Samples (“Prospective Studies”)	715
[2] Research Using Existing Tissue Samples (“Retrospective Studies”)	717
[F] Confidentiality Issues	720
[G] Informing Subjects of Study Results	723
[H] Sharing the Profits from Research	729
§ 17.02 Gene Transfer Research	741
Appendix A: 45 C.F.R Part 46	A-1
Appendix B: Expedited Review Criteria	B-1
Appendix C: Comparison of FDA and DHHS Regulations	C-1
Appendix D: The Nuremberg Code	D-1
Appendix E: The Declaration of Helsinki	E-1
Appendix F: The Belmont Report	F-1
Author Index	AI-1
Index	I-1
Table of Cases	TC-1