Oncology Clinical Trials
Oncology Clinical Trials
Successful Design, Conduct, and Analysis

Second Edition

Editors

William Kevin Kelly, DO
Professor
Department of Medical Oncology and Urology;
Director
Division of Solid Tumor Oncology
Thomas Jefferson University;
Associate Director of Clinical Research
Sidney Kimmel Cancer Center
Philadelphia, Pennsylvania

Susan Halabi, PhD
Professor
Department of Biostatistics & Bioinformatics
Duke University
Durham, North Carolina

© Springer Publishing Company
We dedicate this book to the mentors, collaborators, researchers, and, most importantly, those patients who participate in clinical trials. These patients are not only scientific collaborators but, in many ways, are the ones who make the greatest contribution to the advancement of our collective quest to conquer cancer.

All royalties from this book have been donated to the American Society of Clinical Oncology to support the next generation of cancer researchers to ensure we continue our fight against cancer.
Contents

Contributors xi
Foreword Clifford A. Hudis, MD and Richard L. Schilsky, MD xxi
Preface xxiii
Share Oncology Clinical Trials: Successful Design, Conduct, and Analysis, Second Edition

PART I. BACKGROUND AND INTRODUCTION TO ONCOLOGY CLINICAL TRIALS

1. The Changing Landscape of Clinical Research and Trials 2
   Susan Halabi and William Kevin Kelly
2. Historical Perspectives of Oncology Clinical Trials 7
   Ada H. Braun and David M. Reese
3. Ethical Principles Guiding Clinical Research 13
   Jackson Bruce Smith
4. Industry Collaboration When Developing Novel Agents in Oncology 24
   Hong Xie
5. The Trials and Tribulations of Writing and Conducting an Investigator Initiated Trial 33
   Jake Vinson, Josh Buddle, Julie Filipenko, Christine Tran, Kristofer Prepelica, and Sarah Wise
6. Writing a Consent Form 40
   Christine Grady
7. Why Do Clinical Trials Fail? 48
   Laurence Collette, Jan Bogaerts, and Xavier Paoletti

PART II. DESIGNING ONCOLOGY CLINICAL TRIALS

8. Choice of Endpoints in Cancer Clinical Trials 64
   Mei-Yin Polley, Wenting Wu, and Daniel J. Sargent
9. Design, Testing, and Estimation in Clinical Trials 72
   Barry Kurt Moser
10. Innovative Phase I Clinical Trials 85
    Nolan A. Wages
11. Pharmacokinetics in Clinical Oncology 98
    Jill M. Kolesar
12. Dose Finding Using the Continual Reassessment Method 108
    Mark R. Conaway
13. Design of Phase II Trials 113
    Hongkun Wang and Gina R. Petroni
14. Biomarkers in Confirmatory Clinical Trials 122
   Thomas Gwise
15. Bayesian Designs in Clinical Trials 131
   Gary L. Rosner, B. Nebiyou Bekele, and Yuan Ji
16. Selection Designs 143
   Suzanne E. Dahlberg
17. Phase III Oncology Clinical Trials 148
   Antje Hoering and John Crowley
18. Design of Noninferiority Trials in Oncology 159
   Lei Nie and Zhiwei Zhang
19. Design of Quality of Life Studies 165
   Amylou C. Dueck and Katie L. Kunze
20. Adaptive Designs 176
   Tze L. Lai, Ying Lu, and Ka Wai Tsang

PART III. CONDUCTING ONCOLOGY CLINICAL TRIALS

21. Randomization 188
   Susan Groshen
22. Case Report Form Development 198
   Susan Barry
23. Monitoring, Assessing, and Reporting Adverse Events 207
   Amy Callahan, Elizabeth Ness, and Helen Chen
24. Dose Modification and Use of Ancillary Treatments in Investigational Studies in Clinical Trials 221
   Yoshihito David Saito, Pamela Harris, Ming Poi, and Robert Wesolowski
25. Assessment of Patient-Reported Outcomes in Industry-Sponsored Clinical Trials 233
   Ari Gnanasakthy and Ethan Basch
26. Recruitment of Research Participants 247
   Christopher Gantz
27. Barriers to Oncology Clinical Trials 251
   Chethan Ramanurthy and Yu-Ning Wong
28. The Role of Novel Imaging Techniques in Clinical Trials 258
   Binsheng Zhao and Lawrence H. Schwartz
29. Practical Issues With Correlative Studies 270
   David McConkey and Woonyoung Choi
30. The Development of Companion Diagnostics in Oncology Clinical Trials 277
   Zixuan Wang and Stephen C. Peiper

PART IV. ANALYZING RESULTS OF ONCOLOGY CLINICAL TRIALS

31. Interim Analysis and Data Monitoring 290
   Scott R. Evans and William T. Barry
32. Reporting of Results: Data Analysis and Interpretation 303
   Donna Niedzwiecki
33. Statistical Considerations for Developing and Validating Prognostic Models of Clinical Outcomes 313
   Susan Halabi and Lira Pi

© Springer Publishing Company
34. Statistical Evaluation of Surrogate Endpoints in Cancer Clinical Trials 323
   Marc Buyse, Geert Molenberghs, Xavier Paoletti, Koji Oba, Ariel Alonso, Wim Van der Elst, and Tomasz Burzykowski

35. Development and Validation of Genomic Signatures 336
   Stefan Michiels, Nils Termes, and Federico Rotolo

36. Competing Risks Analysis in Clinical Trials 346
   Solange Bassale, Jeong Youn Lim, and Motomi Mori

37. Systematic Reviews and Meta-Analysis 354
   Claire Vale, Sarah Burdett, David Fisher, Larysa Rydzewska, and Jayne Tierney

38. Statistical Methods for Genomics-Driven Clinical Studies 369
   Richard Simon

39. Handling Missing Data in Oncology Clinical Trials 375
   Xiaoyun (Nicole) Li, Cong Chen, and Xiaoyin (Frank) Fan

PART V. SPECIAL CONSIDERATIONS IN ONCOLOGY CLINICAL TRIALS

40. Health-Related Quality of Life Studies in International Randomized Controlled Oncology Clinical Trials 386
   Andrew Bottomley, Corneel Coens, Murielle Mauer, Madeline Pe, and Francesca Martinelli

41. The Economics of Oncology Clinical Trials 393
   Michaela A. Dinan and Shelby D. Reed

42. Special Considerations in Immunotherapy Trials 399
   Claire F. Friedman, Katherine S. Panageas, and Jedd D. Wolchok

43. Special Considerations in Radiation Therapy Trials 410
   Amanda J. Walker, Hyun Kim, Paul G. Kluetz, Julia A. Beaver, Gideon Blumenthal, and Richard Pazdur

44. Clinical Trials in Hematologic Malignancies 419
   Neil Palmisiano, Bradley M. Haverkos, Sameh Gaballa, Joanne Filicko-O’Hara, Pierluigi Porcu, and Margaret Kasner

45. Issues in Recruiting Elderly, Underserved, Minority, and Rural Populations (and Solutions) 428
   Cecilia R. DeGraffenreid, Jill Oliveri, Chasity Washington, Cathy Tatum, and Electra D. Paskett

46. Telemedicine and Clinical Trials 441
   Ana Maria Lopez

PART VI. COOPERATIVE GROUPS, REGULATORY AND GOVERNING BODIES

47. Cooperative Groups and Global Clinical Trials in the Future 452
   Cooperative Groups: An American and Canadian Perspective 452
      Joseph A. Sparano, Judith Manola, and Robert L. Comis
   Cooperative Groups: A Japanese Perspective 463
      Kenichi Nakamura, Harubiko Fukuda, and Yasuo Ohashi
   Cooperative Groups: The Australian Perspective 476
      Prudence A. Francis, Katrin Sjoquist, and Linda Milesbkin
   Cooperative Groups: A Latin American Perspective 483
      Gustavo Werutsky
   The Evolution of Oncology Drug Evaluation at the FDA 489
   Steven J. Lemery, Gideon Blumenthal, Paul G. Kluetz, Patricia Keegan, Amy McKee, and Richard Pazdur
   The Evolution of the Drug Evaluation Process in the EU 499
   Francesco Pignatti, Emmanuelle Kempf, and Pierre Demolis
   The Evolution of the Drug Evaluation Process in Japan 507
   Hiroyuki Sato, Tomohiro Yamaguchi, Yuki Ando, and Takahiro Nonaka

49. Clinical Trials in the Year 2025 516
   Apostolia M. Tsimberidou, Peter Müller, and Richard L. Schilsky

Index 527
Contributors

Ariel Alonso, PhD
Professor of Biostatistics
Interuniversity Institute for Biostatistics and Statistical
Bioinformatics (I-BioStat)
KU Leuven
Leuven, Belgium

Yuki Ando, PhD
Senior Scientist for Biostatistics
Pharmaceuticals and Medical Devices Agency
Tokyo, Japan

Susan Barry, BS
Senior Project Manager
Office of Clinical Research
Dana-Farber Cancer Institute
Boston, Massachusetts

William T. Barry, PhD
Assistant Professor of Medicine
Department of Biostatistics and Computation Biology
Dana-Farber Cancer Institute
Boston, Massachusetts

Ethan Basch, MD, MSc
Professor of Medicine
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, North Carolina

Solang Bassale, MS
Senior Biostatistician
Biostatistics Shared Resource
Knight Cancer Institute
Oregon Health & Science University
Portland, Oregon

Julia A. Beaver, MD
Acting Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
United States Food and Drug Administration
Silver Spring, Maryland

B. Nebiyou Bekele, PhD
Vice President
Biostatistics & Statistical Programming
Gilead Sciences, Inc.
Foster City, California

Gideon Blumenthal, MD
Acting Deputy Office Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
United States Food and Drug Administration
Silver Spring, Maryland

Jan Bogaerts, MSc, PhD
Scientific Director
European Organisation for Research and Treatment of
Cancer (EORTC)
Brussels, Belgium

Andrew Bottomley, PhD
Assistant Director and Head of Quality of Life
Department
EORTC
Brussels, Belgium

Ada H. Braun, MD, PhD
Executive Director, Regulatory Affairs
Pharmacyclics
Sunnyvale, California

Josh Buddle
Clinical Research Manager
The Prostate Cancer Clinical Trials Consortium
New York, New York

Sarah Burdett, MSc
Senior Research Scientist
Medical Research Council Clinical Trials Unit at
UCL
London, UK
Tomasz Burzykowski, PhD
Professor of Biostatistics (Hasselt University)
Vice-President of Research (IDDI)
Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BioStat)
Hasselt University
Hasselt, Belgium;
International Drug Development Institute (IDDI)
Louvain-la-Neuve, Belgium

Marc Buyse, ScD
Chief Scientific Officer (IDDI)
Associate Professor of Biostatistics (Hasselt University)
International Drug Development Institute (IDDI)
San Francisco, California;
Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BioStat)
Hasselt University
Hasselt, Belgium

Amy Callahan, DNP, APRN, RN, AOCNS
Nurse Manager
Telemetry and Oncology
Paoli Hospital
Mainline Health
Paoli, Pennsylvania

Cong Chen, PhD
Director
Biostatistics and Research Decision Sciences
Merck & Co., Inc.
Kenilworth, New Jersey

Helen Chen, MD
Associate Chief, Investigational Drug Branch
Cancer Therapy Evaluation Program
National Cancer Institute
Rockville, Maryland

Woonyoung Choi, PhD
Assistant Professor
Department of Urology
Johns Hopkins Greenberg Bladder Cancer Institute
Brady Urological Institute
Baltimore, Maryland

Corneel Coens, MSc
Biostatistician
EORTC
Brussels, Belgium

Laurence Collette, PhD, MSc
Head of Statistics
Statistics Department
European Organisation for Research and Treatment of Cancer (EORTC)
Brussels, Belgium

Robert L. Comis, MD†
Co-Chair
ECOG-ACRIN Research Group
Philadelphia, Pennsylvania

Mark R. Conaway, PhD
Professor
Division of Translational Research and Applied Statistics
Department of Public Health Sciences
University of Virginia School of Medicine
Charlottesville, Virginia

John Crowley, PhD
Founder and Chief of Strategic Alliances
Cancer Research and Biostatistics
Seattle, Washington

Suzanne E. Dabbling, PhD
Senior Research Scientist
Department of Biostatistics and Computational Biology
Dana-Farber Cancer Institute
Harvard T. H. Chan School of Public Health
Boston, Massachusetts

Cecilia R. DeGraffinreid, MHS, RHIA
Program Director
Department of Population Sciences
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Pierre Demolis, MD, PhD
Chairman
Oncology Working Party of the Committee for Medicinal Products for Human Use, European Medicines Agency;
Director
Oncology and Haematology Division
French Medicines Agency (ANSM)
London, UK

Michaela A. Dinan, PhD
Assistant Professor
Division of Medical Oncology
Duke Cancer Institute
Duke Clinical Research Institute
Duke University
Durham, North Carolina

Amylou C. Dueck, PhD
Associate Professor of Biostatistics
Department of Health Sciences Research
Mayo Clinic
Scottsdale, Arizona

†Deceased.
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott R. Evans, PhD, MS</td>
<td>Director, Biostatistics Center</td>
<td>George Washington University, Rockville, Maryland</td>
</tr>
<tr>
<td>Sameh Gaballa, MD</td>
<td>Assistant Professor</td>
<td>Thomas Jefferson University, Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Xiaoyin (Frank) Fan, PhD</td>
<td>Director</td>
<td>The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Christopher Gantz, MBA</td>
<td>Program Manager</td>
<td>The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Joanne Filicko-O’Hara, MD</td>
<td>Associate Professor</td>
<td>Thomas Jefferson University, Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Ari Gnanasakthy, MSc, MBA</td>
<td>Principal Scientist</td>
<td>RTI Health Solutions, Research Triangle Park, North Carolina</td>
</tr>
<tr>
<td>Christine Grady, RN, PhD</td>
<td>Chair</td>
<td>National Institutes of Health Clinical Center, Bethesda, Maryland</td>
</tr>
<tr>
<td>Susan Groshen, PhD</td>
<td>Professor</td>
<td>University of Southern California/Keck School of Medicine</td>
</tr>
<tr>
<td>Thomas Guise, PhD</td>
<td>Deputy Director</td>
<td>National Institutes of Health Clinical Center, Bethesda, Maryland</td>
</tr>
<tr>
<td>Prudence A. Francis, MD, MBBS, BMedSc</td>
<td>Medical Oncology Department</td>
<td>St. Vincent's Hospital, The University of Melbourne, Victoria, Australia; Australia and New Zealand Breast Cancer Trials Group, New South Wales, Australia</td>
</tr>
<tr>
<td>David Fisher, MSc</td>
<td>Statistician</td>
<td>Medical Research Council Clinical Trials Unit at UCL, London, UK</td>
</tr>
<tr>
<td>Clare E. Friedman, MD</td>
<td>Assistant Attending</td>
<td>Memorial Sloan Kettering Cancer Center, New York, New York</td>
</tr>
<tr>
<td>Haruhiko Fukuda, MD</td>
<td>Director</td>
<td>National Cancer Center, Tokyo, Japan</td>
</tr>
<tr>
<td>Bradley M. Haverkos, MD, MPH</td>
<td>Assistant Professor</td>
<td>University of Colorado, Denver, Colorado</td>
</tr>
<tr>
<td>Susan Halabi, PhD</td>
<td>Professor</td>
<td>Duke University, Durham, North Carolina</td>
</tr>
<tr>
<td>Pamela Harris, MD</td>
<td>Medical Officer</td>
<td>National Cancer Institute, Rockville, Maryland</td>
</tr>
<tr>
<td>Julie Filipenko</td>
<td>Director</td>
<td>The Prostate Cancer Clinical Trials Consortium, New York, New York</td>
</tr>
<tr>
<td>Julie Filipenko</td>
<td>Director</td>
<td>The Prostate Cancer Clinical Trials Consortium, New York, New York</td>
</tr>
<tr>
<td>Joanne Filicko-O’Hara, MD</td>
<td>Associate Professor</td>
<td>Thomas Jefferson University, Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Ari Gnanasakthy, MSc, MBA</td>
<td>Principal Scientist</td>
<td>RTI Health Solutions, Research Triangle Park, North Carolina</td>
</tr>
<tr>
<td>Christine Grady, RN, PhD</td>
<td>Chair</td>
<td>National Institutes of Health Clinical Center, Bethesda, Maryland</td>
</tr>
<tr>
<td>Susan Groshen, PhD</td>
<td>Professor</td>
<td>University of Southern California/Keck School of Medicine</td>
</tr>
<tr>
<td>Thomas Guise, PhD</td>
<td>Deputy Director</td>
<td>National Institutes of Health Clinical Center, Bethesda, Maryland</td>
</tr>
<tr>
<td>Prudence A. Francis, MD, MBBS, BMedSc</td>
<td>Medical Oncology Department</td>
<td>St. Vincent's Hospital, The University of Melbourne, Victoria, Australia; Australia and New Zealand Breast Cancer Trials Group, New South Wales, Australia</td>
</tr>
<tr>
<td>David Fisher, MSc</td>
<td>Statistician</td>
<td>Medical Research Council Clinical Trials Unit at UCL, London, UK</td>
</tr>
<tr>
<td>Clare E. Friedman, MD</td>
<td>Assistant Attending</td>
<td>Memorial Sloan Kettering Cancer Center, New York, New York</td>
</tr>
<tr>
<td>Haruhiko Fukuda, MD</td>
<td>Director</td>
<td>National Cancer Center, Tokyo, Japan</td>
</tr>
<tr>
<td>Bradley M. Haverkos, MD, MPH</td>
<td>Assistant Professor</td>
<td>University of Colorado, Denver, Colorado</td>
</tr>
<tr>
<td>Name</td>
<td>Title/Position</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Antje Hoering, PhD</strong></td>
<td>President and Chief Executive Officer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cancer Research and Biostatistics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seattle, Washington</td>
<td></td>
</tr>
<tr>
<td><strong>Yuan Ji, PhD</strong></td>
<td>Assistant Vice President</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Program for Computational Genomics &amp; Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NorthShore University HealthSystem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evanston, Illinois;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Professor (part time, Biostatistics)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Public Health Sciences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The University of Chicago</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chicago, Illinois</td>
<td></td>
</tr>
<tr>
<td><strong>Margaret Kasner, MD, MSCE</strong></td>
<td>Associate Professor of Medical Oncology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Director, Acute Leukemia Program</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sidney Kimmel Cancer Center</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thomas Jefferson University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Philadelphia, Pennsylvania</td>
<td></td>
</tr>
<tr>
<td><strong>Patricia Keegan, MD</strong></td>
<td>Division Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Office of Hematology and Oncology Products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Center for Drug Evaluation and Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silver Spring, Maryland</td>
<td></td>
</tr>
<tr>
<td><strong>William Kevin Kelly, DO</strong></td>
<td>Professor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Medical Oncology and Urology;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Division of Solid Tumor Oncology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thomas Jefferson University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associate Director of Clinical Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sidney Kimmel Cancer Center</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Philadelphia, Pennsylvania</td>
<td></td>
</tr>
<tr>
<td><strong>Emmanuelle Kempf, MD, MSc</strong></td>
<td>Department of Medical Oncology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Henri Mondor Teaching Hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creteil, France</td>
<td></td>
</tr>
<tr>
<td><strong>Hyun Kim, MD</strong></td>
<td>Assistant Professor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Radiation Oncology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Washington University School of Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>St. Louis, Missouri</td>
<td></td>
</tr>
<tr>
<td><strong>Paul G. Kluetz, MD</strong></td>
<td>Associate Director for Clinical Science</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Office of Hematology and Oncology Products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Center for Drug Evaluation and Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acting Associate Director of Patient Outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oncology Center of Excellence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silver Spring, Maryland</td>
<td></td>
</tr>
<tr>
<td><strong>Jill M. Kolesar, PharmD</strong></td>
<td>Professor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>College of Pharmacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University of Kentucky</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lexington, Kentucky</td>
<td></td>
</tr>
<tr>
<td><strong>Katie L. Kunze, PhD</strong></td>
<td>Biostatistician</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Health Sciences Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scottsdale, Arizona</td>
<td></td>
</tr>
<tr>
<td><strong>Tze L. Lai, PhD</strong></td>
<td>Professor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Statistics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stanford University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palo Alto, California</td>
<td></td>
</tr>
<tr>
<td><strong>Steven J. Lemery, MD, MHS</strong></td>
<td>Lead Medical Officer (Team Leader)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Office of Hematology and Oncology Products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Center for Drug Evaluation and Research</td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silver Spring, Maryland</td>
<td></td>
</tr>
<tr>
<td><strong>Xiaoyun (Nicole) Li, PhD</strong></td>
<td>Principal Scientist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biostatistics and Research Decision Sciences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merck &amp; Co., Inc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kenilworth, New Jersey</td>
<td></td>
</tr>
<tr>
<td><strong>Jeong Youn Lim, PhD</strong></td>
<td>Assistant Staff Scientist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biostatistics Shared Resource</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knight Cancer Institute</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oregon Health &amp; Science University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Portland, Oregon</td>
<td></td>
</tr>
<tr>
<td><strong>Ana Maria Lopez, MD, MPH, FACP</strong></td>
<td>Associate Vice President for Health Equity and Inclusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University of Utah Health Sciences;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associate Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collaboration and Engagement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Utah Center for Clinical and Translational Science;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Huntsman Cancer Institute</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Internal Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University of Utah School of Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salt Lake City, Utah</td>
<td></td>
</tr>
<tr>
<td><strong>Ying Lu, PhD</strong></td>
<td>Professor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Department of Biomedical Data Science</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stanford University</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palo Alto, California</td>
<td></td>
</tr>
</tbody>
</table>

© Springer Publishing Company
This is a sample from ONCOLOGY CLINICAL TRIALS: SUCCESSFUL DESIGN, CONDUCT, AND ANALYSIS, SECOND EDITION

VISIT THIS BOOK’S WEB PAGE  BUY NOW

© Springer Publishing Company
Shelby D. Reed, PhD, RPh
Professor
Department of Medicine
Duke Clinical Research Institute
Duke University
Durham, North Carolina

Richard L. Schilsky, MD, FACP, FASCO
Senior Vice President and Chief Medical Officer
American Society of Clinical Oncology
Alexandria, Virginia

Lawrence H. Schwartz, MD
James Picker Professor and Chairman
Department of Radiology
Columbia University Medical Center
New York, New York

Richard Simon, DSc
Division of Cancer Treatment and Diagnosis
Director, Biometric Research Program
Chief, Computational & Systems Biology Branch
National Cancer Institute, National Institutes of Health
Rockville, Maryland

Katrin Sjoquist, BSc (Med), MBBS, MClinT(R)
Australasian Gastro-Intestinal Trials Group
Australia New Zealand Gynaecological Oncology Group
National Health & Medical Research Council (NHMRC) Clinical Trials Centre
The University of Sydney
New South Wales, Australia

Jackson Bruce Smith, MD
Emeritus Professor of Medicine
Thomas Jefferson University
Sidney Kimmel College of Medicine
Philadelphia, Pennsylvania

Joseph A. Sparano, MD
Associate Chairman
Department of Oncology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York

Cathy Tatum, MA
Program Director
Department of Population Sciences
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Hiroyuki Sato, PhD
Biostatistics Reviewer
Office of New Drug V Pharmaceuticals and Medical Devices Agency
Tokyo, Japan

Daniel J. Sargent, PhD†
Ralph S. and Beverley E. Caulkins Professor of Cancer Research
Chair of the Division of Biomedical Statistics and Informatics
Department of Health Sciences Research
Mayo Clinic
Rochester, Minnesota

Hiroyuki Sato, PhD
Biostatistics Reviewer
Office of New Drug V Pharmaceuticals and Medical Devices Agency
Tokyo, Japan

†Deceased.
Amanda J. Walker, MD
Acting Associate Director of Radiation Oncology Oncology Center of Excellence;
Medical Officer
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
United States Food and Drug Administration
Silver Spring, Maryland

Hongkun Wang, PhD
Associate Professor
Department of Biostatistics, Bioinformatics &
Biomathematics
Georgetown University
Washington, DC

Zixuan Wang, PhD
Associate Professor
Departments of Surgery and Pathology, Anatomy and
Cell Biology
Sidney Kimmel Medical College, Thomas Jefferson
University
Philadelphia, Pennsylvania

Chasity Washington, MPH
Director
Center for Cancer Health Equity
The Ohio State University James Cancer Hospital and
Solove Research Institute
Columbus, Ohio

Gustavo Werutsky, MD
Latin American Cooperative Oncology Group
Porto Alegre, Brazil

Robert Wesolowski, MD
Assistant Professor
Department of Internal Medicine/Division of Medical
Oncology
Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Sarah Wise, MS
Regulatory and Quality Manager
The Prostate Cancer Clinical Trials Consortium
New York, New York

Jedd D. Wolchok, MD, PhD
Lloyd J. Old/Virginia and Daniel K. Ludwig Chair in
Clinical Investigation
Chief, Melanoma & Immunotherapeutics Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
New York, New York
Foreword

Clinical trials are the engine of progress in the development of new drugs, procedures, and devices for the detection, monitoring, prevention, and treatment of cancer. A well-conceived, carefully designed, and efficiently conducted clinical trial can produce results that change clinical practice; deliver new oncology drugs, interventions, and diagnostics to the marketplace; and expand our understanding of cancer biology. A poorly done trial does little to advance the field or guide clinical practice, consumes precious clinical and financial resources, and challenges the validity of the ethical contract between investigators and the volunteers who willingly give their time and effort to benefit future patients.

In the first edition of their book, Oncology Clinical Trials: Successful Design, Conduct, and Analysis, Kelly and Halabi delivered an outstanding primer that addressed the fundamentals of clinical trial design, execution, analysis, and reporting in easily consumed chapters written by experts in the field. Since publication of the first edition in 2009, much has changed in our approach to cancer treatment and, of necessity, in the methods used to evaluate new agents and devices. The understanding of the cancer genome has led to the recognition that most common tumors are collections of rare molecular subtypes that may have similar histology but can harbor unique molecular drivers, display distinct natural histories, and require targeted treatment approaches. The field of precision medicine has blossomed with the development of molecular diagnostic tests that are increasingly used to interrogate the cancer genome and guide therapy selection as well as trial eligibility. But with these new opportunities have come new challenges in clinical trial design and execution. Simply finding enough patients with rare tumor genotypes to participate in clinical trials is often difficult and expensive. It can require that thousands of patients be screened to find the few with the requisite genotype. The clinical research community has responded with new clinical trial designs aimed at increasing the efficiency of molecularly driven studies and a new lexicon of clinical trial terminology. “Basket” trials, “umbrella” trials, “platform” trials, some using Bayesian or “adaptive” designs that incorporate dynamic randomization, early futility assessment, or “seamless” transition to expanded cohorts have now become commonplace. The execution of these trials is complex and requires unique design elements; near real-time monitoring; rapid data collection; and clear communication among sponsors, investigators, regulators, and study participants about trial modifications over time.

The rapid recent growth of immunotherapy for cancer has already produced long-term remissions in some patients despite their having far-advanced and refractory disease. The rise of immuno-oncology has revealed new patterns of tumor response and progression not well characterized by conventional response criteria and produced new toxicities not well described by standard toxicity grading scales. Thus, new treatment endpoints have begun to emerge that impact the design and execution of clinical trials, and new outcome measures, such as patient-reported outcomes, have become an important source of information about treatment tolerability.

As the investigator community has been challenged to respond to the opportunities and challenges presented by precision medicine and immuno-oncology, so has the global regulatory community been challenged in its assessment of the risks and benefits of these new therapeutic options. In some jurisdictions, new regulatory pathways have been introduced, such as Breakthrough Therapy in the United States and Adaptive Pathways piloted by the European Medicines Agency. In both cases, the goal is to introduce new cancer drugs into clinical use as quickly as possible, particularly in populations with high unmet medical need. Yet doing so may allow drugs into widespread clinical use based on limited data sets from clinical trials performed in highly selected populations. Thus, learning from the use of new agents in the real-world setting is increasingly important to optimize dosing, clarify labeling, and identify patients most or least likely to benefit or at highest risk of severe toxicity. Real-world evidence thus becomes a necessary and important complement to clinical trial data in drug development and evaluation, and we anticipate a deepening of our understanding of its utility and limitations in the next few years.
It is gratifying to see that Kelly and Halabi have produced a second edition of Oncology Clinical Trials that has kept pace with the rapid evolution of cancer treatment approaches. The increased focus on biomarker-driven trials, adaptive trial designs, companion diagnostics, patient-reported outcomes, immunotherapy, rare populations, and the perspective of regulatory agencies are all welcome additions that enhance the fundamental approaches to clinical trial design and execution emphasized in the first edition.

Today’s cancer clinical trials are more complex, more expensive, and subject to more regulatory oversight than ever before. Current and future trainees in clinical research are challenged by enormous clinical demands, a highly competitive funding climate, and an administrative bureaucracy that can delay activation and then conclusion of a research study for months and sometimes years while the science moves on. More than ever, trainees in cancer clinical research need a concise yet comprehensive primer to guide them through the scientific, technical, ethical, and regulatory aspects of performing clinical trials. With this edition, Drs. Kelly and Halabi have again assembled an outstanding group of authors who are uniquely qualified to address the many complexities of cancer clinical trials. Historically, it has taken 10 to 15 years and cost hundreds of millions of dollars to bring a new cancer drug to the market, with only 5% to 8% of drugs that enter clinical testing emerging as marketed products. Hundreds of potential new cancer drugs now flood industry pipelines and, given relatively low rates of trial participation—especially among adults with solid tumors—there simply are not enough patients, dollars, or time to test them all using conventional clinical trial paradigms. As clinical investigators, we have both the opportunity and the responsibility to design trials that are efficient, informative, and robust. In short, we must learn as much as possible from each and every study participant. This book will help investigators achieve these goals and will also stimulate continued innovation in clinical trial design.

As with the first edition, the editors and publisher of this volume have agreed to provide the royalties from the book sales to the Conquer Cancer Foundation of the American Society of Clinical Oncology. Since the inception of the Young Investigator Awards and Career Development Awards programs in 1984, the Conquer Cancer Foundation has provided more than $83 million in support of clinical and translational research undertaken by oncology fellows and junior faculty. Many of the contributors to this book have served as mentors for applicants to these programs, acted as reviewers of submitted applications, or have themselves been grantees. The authors have all contributed in many ways to the education of young clinical researchers and it is fitting that through this work and the proceeds it generates, they will continue to mentor and support the next generation. For that, we should all be most grateful.

Clifford A. Hudis, MD
Richard L. Schilsky, MD
American Society of Clinical Oncology
Alexandria, Virginia
Preface

More than a decade ago, the concept of preserving the experience of many of those researchers that shaped modern oncology came to life in the first edition of *Oncology Clinical Trials: Successful Design, Conduct, and Analysis*. The book was a collaborative effort and brought the knowledge and expertise of leading oncologists, statisticians, and all clinical trial professionals from academia, industry, and government together to share their experience in designing, conducting, analyzing, and reporting clinical trials in cancer. This allowed these seasoned investigators to pass on their knowledge to those who are entering the field and those already engaged in research to expand their knowledge base. In so doing, our mission was to enhance the successful design, development, management, and analysis of oncology clinical trials for the next generation and beyond.

Since the book was published eight years ago, there has been an exponential growth in our understanding in the biology that underlies the growth of malignancies that has accelerated the number of novel agents entering into the clinic. This has increased the complexities of clinical trials, requiring innovative trial designs and more sophisticated methods to screen, enroll, treat, collect, and analyze the data. These new therapies also taught us how we need to monitor patient safety and gauge the effectiveness of a therapy differently than in the past. This has been paralleled by a tremendous effort from the regulatory agencies to streamline the new drug approval process which not only ensures safety for patients but also provides breakthrough therapies to patients quicker. Results have been astonishing: more drugs that treat and prevent the suffering of cancer have been approved for patients in the past 8 years than in the preceding 20 years.

While this book focuses on oncology clinical trials, the fundamental concepts and basic principles are applicable to all trials in many medical disciplines. We hope that this work will aid the junior investigator’s academic, industry, or government career in order to improve the quality of clinical trials. In so doing, their discoveries can be quickly and efficiently translated into improved patient outcomes and future care.

The views expressed in the book are solely those of the contributors and do not represent those of the organizations or of the universities that the authors are affiliated with. In addition, the authors accept all responsibility for any errors or omissions in this work.

*William Kevin Kelly, DO*

*Susan Halabi, PhD*
Why Do Clinical Trials Fail?

Laurence Collette, Jan Bogaerts, and Xavier Paoletti

INTRODUCTION

Failure is a concept that will shift with perspective. For new pharmaceutical entities for which access to market is sought, failure has the connotation of “not making it.” For trials studying important unanswered questions in the medical setting, failure could have a different meaning of “not answering the question to a satisfying degree.” There are also other types of failure, with varying degrees of incurred damage. Trial failure may include features such as misleading the community, which is an especially nasty way of failing to answer the question, or failure by lack of quality. In this chapter, we discuss trial failure in various forms and propose some prevention measures to help avoid failure. First, however, we discuss how failure affects different interested stakeholders and what the costs of these types of failure are (Table 7.1).

Admittedly this table is a messy undertaking, but we feel it can be an interesting model to discuss the outcomes of various types of failure. To a large extent, the stakes of various parties (the patients in the study, population with the disease, medical community, public health system, and investors in the pharmaceutical industry) are the same. We all want safe and effective treatments to be available in as brief a time as possible to correctly selected patients for a reasonable price. What we have tried to highlight in the table are some of the differential outcomes of failure types with regards to stakeholder groups, magnifying them beyond the background of the common good. The reader may come up with their own interpretation of the entries in this table. We wanted to make it available as a model of thinking about failure.

The following examples illustrate our proposed use of the table:

- If a trial never enrolled any patients, this may mean the question was not applicable; the patient population did not sustain any effect from that failure, but the scientific community and the financiers of that trial certainly lost from it. Even the patients indirectly suffered because the community set up to research the question was spending efforts on the wrong question.
- Erroneous conclusions from a trial may actually benefit the financial investor, while setting up patients with a suboptimal treatment, leading the scientific community astray, and not providing best value for money for the health system.
- Drawing conclusions too early from an ongoing trial (stopping the trial) may lead to vastly different outcomes, ranging from early acceptance of a good drug (where everybody benefits) to the whole community being stuck with inconclusive data, while being unable to repeat the experiment.
- Another failure type that deserves highlighting is the case where the research was good, but nothing happened with the conclusions. The world has experienced this in the past 65 years, with the very slow implementation of antismoking policies after the proof that smoking leads to lung cancer in 1950 (1).

The following sections further discuss several types of failure with illustrative examples and make recommendations to help avoid them.

FAILURE RESULTING FROM LACK OF RECRUITMENT

By far the most common reference to “trial failure” is when a trial cannot recruit the number of patients needed to test the hypothesis that it was designed to test. We detail in this section several circumstances that may lead to difficulties in completing accrual to (mostly randomized) studies.

Failure Because the Randomization is Too Challenging for the Patients

Trials that were designed to address clinical questions of extreme interest for the medical community
### TABLE 7.1 Taxonomy of Trial Failure

<table>
<thead>
<tr>
<th>Failure Type*</th>
<th>Cost of Failure by Stakeholder†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (on and off trial)</td>
</tr>
<tr>
<td>The trial is needed but is never done (or too late, leading to no enrollment)</td>
<td>May be very high</td>
</tr>
<tr>
<td>Wrong control arm or controversial control arm</td>
<td>Participation loses benefit</td>
</tr>
<tr>
<td>Wrong end point(s)</td>
<td>Participation loses benefit</td>
</tr>
<tr>
<td>Wrong timing (too early or too late) Nonexistent or disappearing population (too late) Trial uses wrong assumptions (too early)</td>
<td>No effect</td>
</tr>
<tr>
<td>Insufficient or misleading upfront biomarker science</td>
<td>Participation loses benefit</td>
</tr>
<tr>
<td>Failure to enroll</td>
<td>No effect for nonparticipants Population may lose benefit of learning</td>
</tr>
<tr>
<td>Low recruitment but only trial of its kind</td>
<td>Decreased benefit</td>
</tr>
<tr>
<td>Impossibility to reach number of events (lack of power)</td>
<td>May miss an effective drug</td>
</tr>
<tr>
<td>Lack of quality (surgery, biomarker work)</td>
<td>Suboptimal treatment</td>
</tr>
<tr>
<td>The “negative trial”</td>
<td>No effect</td>
</tr>
<tr>
<td>Failure to convince When “significant” data do not lead to significant change Phase I does not inform correctly the phase II dose</td>
<td>Can be huge Toxicity, lack of effect</td>
</tr>
<tr>
<td>Convincing—but wrong—conclusions, leading to erroneous development program</td>
<td>Can be huge</td>
</tr>
<tr>
<td>Poor interim decisions leading to disclosing significant results too early (e.g., on nonfinal end point)</td>
<td>Too optimistic messages, drug on the market may not be good</td>
</tr>
</tbody>
</table>

(continued)
TABLE 7.1 Taxonomy of Trial Failure (continued)

<table>
<thead>
<tr>
<th>Failure Type*</th>
<th>Cost of Failure by Stakeholder*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too many questions in one trial</td>
<td>Patients (on and off trial)</td>
</tr>
<tr>
<td></td>
<td>Confusion – difficulty for next developments</td>
</tr>
</tbody>
</table>

*This column is loosely ordered by the time of the failure, from concept to final interpretation.
†This table indicates some possibilities for the various stakeholders but is not exhaustive. The description is necessarily short and must be seen as one of many outcomes.

paradoxically seem to not be exempt of the risk of failure to recruit patients. A striking example is the yet impossible realization of a randomized controlled trial to compare radical prostatectomy with radical radiotherapy for localized prostate cancer. The two therapeutic approaches, which are well established in clinical practice, are regarded as bearing similar long-term oncologic outcome but are associated with different side-effect profiles. Yet the best available evidence to inform head-to-head comparison of these concurrent approaches relies on retrospective, matched case-control studies (2) and a few prospective population cohort studies (3).

Traditionally, studies that compared a same treatment started immediately or deferred to signs of disease progression proved difficult to conduct. One example is the randomized Eastern Cooperative Oncology Group study EST 3886 (4) that aimed to compare immediate versus deferred adjuvant hormonal therapy for patients with positive lymph nodes after radical prostatectomy and lymphadenectomy: 36 institutes in the United States altogether randomized only 98 patients in 1988–1993. The trial was then closed, but it so far remains the sole reliable comparison supporting the current treatment guidelines for this group of patients. Similarly, a European Organization for Research and Treatment of Cancer (EORTC) trial that tested the same questions for patients with positive lymph nodes for whom the radical prostatectomy was abandoned (5), recruited very slowly and was eventually closed after 12 years of recruitment and 234 patients randomized, not reaching its target sample size. Similarly, the intergroup study testing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder recruited with difficulty, although it recruited across 12 European countries and Canada (6). In all these examples, lack of enthusiasm resided in good part on the side of the patients, who had strong preference for either being offered treatment shortly after diagnosis or being spared therapy and its side effects for as long as possible. This issue highlights a particularly difficult area of clinical trial research, where the medical community is considering potential reduction of treatment or a drastic change in treatment a potentially viable option, but finding it difficult to implement the necessary research to obtain proof of the potential significant change in practice. Patients may find it impossible to accept randomization between being treated or not being treated (immediately) or between two different modes of treatment. Indeed, the medical community may not be optimally conducive to such research because of siloing, hospital processes, and habit.

Failure Because the Clinicians Have Conflicting Interests

However, clinician views may also strongly affect trial feasibility. In 2000, the EORTC genitourinary group launched a phase III trial (EORTC 30004) to evaluate if chemotherapy with 4 weekly intravesical instillations of mitomycin-C could substitute for the existing practice of transurethral resection (TUR) followed by 1 single immediate instillation of mitomycin-C for solitary low noninvasive bladder cancer. The study aimed for 1,000 patients and was closed after 3 years and several attempts to facilitate recruitment, with only 58 patients recruited from 12 centers. Interestingly, the same group had recruited 512 patients over a period of just 3 years in their former trial in the same indication (7). The EORTC trial failed to recruit despite amendments and surveys at the centers that aimed to broaden entry criteria and facilitate patient access to the trial.

The true reason for the failure ironically is written in the study protocol itself. The introduction ends by the premonitory statement that “The philosophy of this trial, that is to question the value of TUR, will be difficult for urologists who are surgeons by education and profession. However, evidence based EORTC data, quality of life aspects and health economic reasons make this study...
a unique opportunity to investigate the rationale of ablative intravesical chemotherapy in low risk Ta, T1 bladder cancer. It seems that the perspective that this trial might change practice and reduce the amount of surgical procedures might have hampered the willingness to recruit patients in the study. A similar trial was attempted in the United Kingdom in the mid-2000s and failed the same way. Since then, the multidisciplinary approach made its way to the clinics. Interestingly enough, a new study, called CALIBER (8), was launched in the United Kingdom by the Institute of Cancer Research in January 2015 to address the very question. The study is a randomized, multicenter, phase II feasibility study that aims to recruit 174 patients from approximately 25 UK sites over 3 years. The study is currently open, and it is recruiting slower than expected but is likely to complete with some delay. Although all of the examples covered here relate to urologic oncology, the problem of recruiting patients in studies testing markedly different treatments is not unique to that specialty.

Experience shows that the risk of randomized trials failing increases as the difference in the types of treatment increases, and when this difference becomes too big, the trials are deemed to fail, irrespective of the relevance of the question (Figure 7.1). Everybody would want to know the result of such a trial, but no one is brave enough to do it.

**Failure Because of Insufficient Coordination Across Departments**

A trial may also fail to recruit because of suboptimal coordination between the medical and specialist departments involved in the process of patient selection. Often, this happens because of failure to refer patients from the unit where the disease is diagnosed to that where the patient may be recruited and treated in the study. Restrictions to eligibility, relating to prior treatments, and time allowed after or documentation of diagnostic procedures (imaging, pathology) are likewise likely to hamper recruitment if communication between departments is not perfectly coordinated. Ideally, all departments should be aware of the study protocol and should support it. For example, if credentialing of a radiation technique via dummy run is required prior to activating a center, it is important that the radiation physics department be involved in the decision to contribute to the study so that they include this contribution in their workload. Failure to organize this coordination results in delays of site activation that directly affect study completion timelines.

**FAILURE BY EXCESS OF COMPLEXITY**

The ongoing study EORTC 22113-LungTech (9) launched by the EORTC radiation oncology group in November 2014 perfectly illustrates the challenges that complex site credentialing and prospective quality assurance represent and how these affect accrual. The study is a single-arm phase II testing image-guided stereotactic body radiotherapy (IG-SBRT) in patients who present with centrally located non–small cell lung tumor 7 cm or less in diameter and are unsuitable or unwilling to undergo surgery. The study is therefore testing a challenging technologically involved potentially curative approach for patients who would otherwise undergo palliative care. The primary measure of effectiveness will be freedom from local progression at 3 years after start of IG-SBRT as assessed by serial computed tomography (CT) scans. To secure patient safety, the protocol requires all centers to perform delineation and radiation treatment planning for benchmark cases and to present valid beam output audit in addition to completing a radiation facility questionnaire. Furthermore, the sites must also be credentialed for the use of their positron emission tomography (PET) scanner, four-dimensional CT, and intensity-modulated radiotherapy techniques via one or more phantoms (Figure 7.2). This is done by means of site visit during which the planning system on the phantom cases is checked.

Figure 7.3 shows the actual and planned recruitment in the study as of November 2016. The vertical blue bars in the figure show that these requirements severely delayed site activation, with less than half of the centers activated at 1 year after study start. In addition,
FIGURE 7.2  Trial 22113 LungTech study scheme. The scheme shows the various steps of central review and quality assurance required to recruit a patient in a center that is credentialed. After informed consent, initial radiologic staging and histologic confirmation, the diagnostic images are uploaded on the European Organization for Research and Treatment of Cancer (EORTC) central server. Two independent reviewers confirm patient eligibility. The radiation treatment planning is performed and uploaded on the EORTC central server for prospective radiotherapy (RT) quality assurance (RTQA). Once the plan adequacy is confirmed, the patient is treated. All radiotherapy images are then uploaded on the EORTC central server for retrospective quality assurance. The patient then proceeds to follow-up. CBCT, cone beam computed tomography; NSCLC, non–small cell lung cancer; SBRT, stereotactic body radiotherapy.

*Staging is based on two-dimensional or three-dimensional FDG-PET/CT.
†If the patient consented to participate to the optional translational research, four-dimensional FDG-PET/CT may be used as imaging coregistration.

FIGURE 7.3 Site activation and patient recruitment in the European Organization for Research and Treatment of Cancer (EORTC) study LungTech from initiation in November 2014 until November 2016.

Several review committees are involved before a patient may be treated (see Figure 7.2). A central review pathology panel confirms histology and a prospective quality assurance program necessitates that centers send their treatment plans for review by an expert committee prior to treating each patient. This results in extreme delay of patient recruitment as shown by the red curve in Figure 7.3. For this type of study, one may either challenge whether all credentialing, quality assurance, and central review procedures are critical to the study and if the tested approach can be translated to the clinical practice. If they are, one may consider adapting study timelines and trial financing.

Missing the Window of Opportunity

Studies may also be abandoned or fail to recruit because they do not come at the right time. For example, studies of ablative chemotherapy in bladder cancer against TUR discussed previously may have been launched too early. Conversely, some studies are launched too late. This may happen when the question addressed by the study becomes irrelevant while the trial is ongoing. An example of this may be when a patient population is redefined on the basis of new knowledge or new diagnostic method, so that the patient group targeted by the study protocol no longer exists as such, or because the study did not collect information about a biomarker that meanwhile has been discovered and strongly affects prognosis and/or response to treatment, such as human papillomavirus status for head and neck cancer. Another example is when the experimental intervention that the study tests is adopted in clinical practice without waiting for clinical trial results—thus in absence of level-1 evidence. Clearly, the likelihood that the study question becomes obsolete increases as the total time the study takes to be initiated and to complete recruitment increases. Conversely, the recruitment rate usually sharply declines as the study relevance decreases.

The LungART study (10) sponsored by the Gustave Roussy Institute in Villejuif, France, offers an example of such circumstances. LungART is a phase III study that tests if postoperative conformal radiotherapy increases disease-free survival compared with no postoperative radiotherapy in patients with completely resected non–small cell lung cancer and mediastinal nodal (N2) involvement. The study needs 700 patients and was scheduled to take at least 10 years of recruitment when it started in February 2007. However, the study has only recruited 60% of its planned number as of November 2016 and despite intergroup collaboration across Europe, it is expected to complete recruitment only by 2021. Reasons for the slow recruitment are several:

1. A number of studies testing adjuvant immuno-therapy for advanced non–small cell lung cancer patients have been launched (e.g., the intergroup study PEARLS in Europe [(11)] and the intergroup study BR31 in Canada [(12)], which are competing partially with the study).
2. A more thorough preoperative staging, including endobronchial ultrasound–guided biopsy and/or mediastinoscopy, reduces the frequency of intraoperative detection of unexpected N2 disease so that the patient population of interest diminishes.
3. Induction chemotherapy is not allowed by the study, thus making a number of patients ineligible.
4. Disappointed by the success rates of upfront surgery and induction chemotherapy with surgery, some centers have reverted to an approach of preoperative radiochemotherapy for their patients with non–small cell lung cancer, thus making them unsuitable for this study.
5. Patient acceptance of the randomization to no adjuvant therapy seems low.

All of these reasons explain why the study is poorly recruiting.

Sometimes, new treatments are adopted in the clinic without formal testing. In most instances, this phenomenon occurs when treatment novelty results from technologic advances, such as intensity-modulated irradiation laparoscopic surgery. Such technologic advances are often a priori regarded as progress. Their implementation requires investment in infrastructure and machines, which once made, results in adoption of the new technique without formal comparative testing.

Clinical interventions do not follow different pathways of diffusion from other innovations. Diffusion of innovation, as modeled by Everett Rogers (13), has five stages: the launch by the (1) innovators followed in successive stages by the (2) early adopters; (3) early majority; (4) late majority; and, finally, (5) laggards (Figure 7.4).
The speed of diffusion accelerates to a peak (the tipping point), which occurs on average at 20% adoption. Studies testing new interventions on a large scale (multicenter, multiregions) are best performed after the technology has been pioneered but before it has been widely adopted. If evaluated too early, the community feels that patient safety and learning curves are insufficiently documented to embark in wide-scale testing. However, once most physicians and centers have adopted the new approach, it is too late because the equipoise required for formal comparative assessment in randomized clinical trials is no longer present. Patients and/or physicians would refuse to enter the study at that time. An objective assessment of the timing of the study with regard to this model of innovation adoption may help launch studies at the right time and maximize success.

**How to Make a Study That Completes Within Timelines**

No sponsor surely wishes to invest in a trial that will never deliver, and a good share of the clinical trial costs are invested at the time of trial conception and implementation. Therefore, an extensive and objective assessment of the true feasibility of trial recruitment within timelines is essential. Besides evaluation of the relevance and appropriateness of the study design by an independent committee of experts, several steps can be taken prior to starting a clinical trial:

- The use of detailed feasibility questionnaires prior to trial launch is strongly recommended. Such questionnaires must address all aspects of the logistics and patient availability at the centers. Elements that feasibility questionnaires should address are listed in Table 7.2 and guidance documents and checklists are available online (14).
- Acceptance of the study by patients is not an element to neglect. Success calls for involvement of patient representatives at every stage of a study development. Indeed, patients representatives are most knowledgeable by their experience, of the concerns of patients who will be proposed to participate in a clinical experiment. Their input provides critical highlights on the feasibility of recruitment. The use of patient survey questionnaires or feasibility of randomization studies is encouraged prior to launching the most challenging studies. It is important to highlight that in the setting of a randomized trial, and as part of informed consent, the investigator is tasked with communicating uncertainty to the patient they are treating. The way the logic of the trial is elaborated, preferably with the help of patients, can be very beneficial (or detrimental) to the ultimate success of the trial.
- Financial support to the centers contributing patients and to the various laboratories and committees involved in the study should be sufficient to cover both the real costs required by the study protocol (such as extra diagnostics or extra visits) and to support the time spent by staff to perform the study. This is usually easier for commercial sponsors who can offer financial compensation as well as data management and other administrative support to the centers. For academic sponsors, the impact of limited financial support must not be underestimated. In this case, it is strongly recommended that commitment to perform a study be obtained at the level of the hospital direction, rather than at the level of a hospital department or by an individual investigator, in order to avoid overoptimistic estimates of recruitment potential based on feasibility questionnaires.
TABLE 7.2  Elements to Consider in Assessing Trial Feasibility at the Recruitment Centers

<table>
<thead>
<tr>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competing studies</td>
</tr>
<tr>
<td>Prior successful experience conducting studies in same indication</td>
</tr>
<tr>
<td>Number of patients with indication seen in the department</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Practical Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation from standard practice</td>
</tr>
<tr>
<td>Equipment required</td>
</tr>
<tr>
<td>Personnel required</td>
</tr>
<tr>
<td>Other departments involved (for referring patients or else)</td>
</tr>
<tr>
<td>Credentialing requirements (material)</td>
</tr>
<tr>
<td>Requirements for central collection or review of samples</td>
</tr>
<tr>
<td>Data management</td>
</tr>
<tr>
<td>Administration</td>
</tr>
<tr>
<td>Training</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptability of randomization to patients</td>
</tr>
<tr>
<td>Benefit-to-risk ratio</td>
</tr>
<tr>
<td>Eligibility criteria</td>
</tr>
<tr>
<td>Source of patients</td>
</tr>
<tr>
<td>Estimates of effective numbers likely to enroll</td>
</tr>
<tr>
<td>Total number that can be screened and screen failure ratio</td>
</tr>
</tbody>
</table>

(continued)
A study should be launched only if it is financially tenable for the participating institutions and if their commitment to perform the study is high, if patient availability and protocol acceptance to patients are high, and if both of these are sufficiently strong to sustain competition from other studies for the same population in the same institutions (Figure 7.5).

Once the study is ongoing, several measures may be envisaged in case of lack of recruitment.

First, the screening logs at the participating institutions must be carefully reviewed to identify any difficulties with the study. Often, delays imposed between diagnostic examinations and patient registration in a study or too-narrow conditions on some measurable parameters may result in exclusion of patients from the study. If patient safety allows, the study eligibility criteria should be relaxed as much as possible. Next, additional sites or intergroup participation must be envisaged, whenever the recruitment capacity of the centers has been overestimated, if the trial remains scientifically relevant. However, this often necessitates additional finances. Protocol procedures may also be simplified, whenever possible. Finally, an Independent Data Monitoring Committee (IDMC) may be called to review the current risk-benefit balance for patients entering the study. The committee may also confirm if the study scientific merit holds despite the delay. In randomized comparative trials, the implementation of formal interim analyses for futility should be discouraged, unless a substantial part of the planned sample

TABLE 7.2  Elements to Consider in Assessing Trial Feasibility at the Recruitment Centers (continued)

<table>
<thead>
<tr>
<th>Study Timelines</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are study timelines for recruitment realistic?</td>
<td>Report if considered not realistic and why.</td>
</tr>
<tr>
<td>Is there support from the department for the whole duration of the study?</td>
<td>Commitment is for several years.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensation to sites</td>
<td>Is compensation sufficient for the institution to support it? Are additional costs incurred by the site not covered that would jeopardize recruitment?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Considerations</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicate any additional considerations that would increase complexity. Indicate any additional considerations of performing the study that would not have been listed previously.</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 7.5  How to select trials that will not fail by lack of accrual.
is already recruited. Indeed, such interim analyses will further decrease the final study power. It is generally not recommended to conduct them early in the information time, when less than 40% of the planned events have been observed (15).

If the study recruitment remains poor, the trial may never recruit the planned number of patients. In that case, options to make the best use of the data that is already collected or that may become available from the patients already recruited in the study must be envisaged. If only very few patients were entered, a short communication about the data may be the only option. However, if a non-negligible number of patients are available, a revision of the statistical analysis plan may be envisaged in order to define new timelines for data analysis or reset achievable secondary objectives. With time-to-event end points, the number of events needed to test the original trial hypothesis at the desired power level may never be reached. In that case, a statistician, possibly with medical experts who have not seen any interim trial results, should propose a plan for data release. This plan may be for testing the original hypothesis at a reduced power (e.g., 70%). If the numbers are too small for any meaningful power level, then the plan may be based on length of follow-up. Further alternatives consist of redefining a noncomparative phase II-type of objective, either based on a secondary end point or on the primary, such as estimating the rate of the end point at a fixed time point. This way, the study may at least inform the design of future studies.

This approach was used in the intergroup study EORTC 40004-CLOCC (16). The study was launched in 2002 as a phase III study and was designed to compare overall survival (OS) in patients with nonresectable colorectal liver metastases randomly assigned to systemic treatment (the comparator arm) or systemic treatment plus radiofrequency ablation (RFA). The plan was to recruit 390 patients over 3 years and to conduct the analysis at year 6, when 317 patients would have died. In March 2005, it became clear that recruitment remained too low, as only 77 patients had been randomized. Because this was the only trial testing RFA in this setting, the study was formally amended to continue as a noncomparative randomized phase II trial. A Fleming one-stage design was implemented in the combination arm, with OS rate at 30 months as the primary end point. The target sample size was reduced to 142 patients so that another 75 patients were needed to be recruited over an additional 1.5 years. Eventually, the study was closed in June 2007, with only 119 patients recruited from 22 hospitals. The first results were published in 2012 (17) with 4.4 years of median follow-up. Despite the lower number of patients, the study met its primary objective with a 30-month OS rate of 61.7% (95% confidence interval [CI], 48.2–73.9) for the combined treatment group. However, results were in the same range for the systemic treatment group so that OS benefit remained uncertain at the time of that analysis. Follow-up of all patients continued, and an update of the study with 9.9 years of median follow-up was presented in 2015 (18). The data then indicated a significant long-term benefit of combined treatment using RFA over systemic treatment in an exploratory comparative assessment (hazard ratio [HR] = 0.58, 95% CI, 0.38–0.88, p = .010). These results raised enthusiasm in further testing this approach in new trials.

**FAILURE IN LATE STAGE: THE PHASE II–TO–PHASE III TRANSITION**

In this section we discuss the risky transition from (late) phase II to phase III.

**Lack of Understanding of a Drug Mechanism of Action**

A number of phase III studies in oncology have failed to meet their primary end point yet have demonstrated marked effects on important secondary end points in all or a subset of the patients. Such results most often lead to controversy in interpretation and as such, often fail to affect clinical practice.

In the mid-1990s, prostate-specific antigen (PSA) appeared to be a promising biomarker for detection and monitoring of progression of prostate cancer. Data also suggested that in patients whose disease no longer responded to hormonal manipulation (castration-resistant prostate cancer or CRPC; the hormone-insensitive refractory setting), a decrease of 50% of the PSA during treatment was associated with OS (19). From that time, phase II trials in this disease setting started using this definition of response as their primary end point. This approached worked well for chemotherapeutic agents. But when the end point was used in a study of 250 patients testing high-dose calcitriol and docetaxel to placebo and docetaxel in CRPC, the study showed no benefit for this end point, but there was a significant benefit in OS (20). It was later understood that this drug effect is not mediated through the same mechanisms as that of cytotoxic agents and that the drug does not lower PSA. The trial end point was thus inadequate to detect effects of this treatment.

Likewise, the first two studies that tested the immunotherapeutic agent sipuleucel-T against placebo in CRPC failed to meet their set primary end point of objective progression-free survival (PFS). In the first trial of 127 patients, the sipuleucel-T group had a significant reduction of the risk of death of 41%, as compared with those in the placebo group (p = .01) (21), whereas the benefit seen in the second study was not statistically significant (22). A further double-blind, placebo-controlled, multicenter trial, called the Immunotherapy