Index

A
Abbott Laboratories, 8, 9
Adaptations. See Design adaptations:
   Operational adaptations
Adaptive, defined, 29
Adaptive enrollment:
   advertising tactics, 125, 126
   basic requirements for managing, 119–120
   defined, 3, 223
   as element in eight-point program for
      embracing adaptive approach, 264
   facilitating information collection, 120
   identifying recruitment successes, 122
   key metrics, 121
   as operational adaptation issue, 116, 117,
      119–127, 223, 248–249
   reporting information, 123–124
   screen failures, 33, 38, 121, 122, 125, 126,
      161
   STD study example, 124–125
   tracking progress, 121
   value of early knowledge, 33–34
Adaptive monitoring
   in agile confirmatory phase, 166, 168–169,
      170
   in agile efficacy phase, 159–160
   background, 3–4
   comparative cost of site visits, 130–131
   defined, 3, 223
   as element in eight-point program for
      embracing adaptive approach, 264
   flexible team approach, 131–132
   as operational adaptation issue, 130–135,
      159–160, 166, 168–169, 223, 249
   role in efficient site closeout and database
      lock, 138–138
   role of technology, 132–135
Adaptive randomization
   background, 101
   Bayesian technique, 103
   case study using Pocock-Simon biased-coin procedure, 103–104
   case study using response-adaptive
      procedure, 104–105
   case study using urn-adaptive biased-coin
      procedure, 104
   covariate-adaptive, 101, 102
   as data capture technology, 237–238
   infrastructure for, 103
   response-adaptive, 102, 104–105
   treatment-adaptive, 101, 102
Adaptive research. See also Agile clinical development
   advantages in dose-finding trials, 75
   background, 29–33
   compared with group sequential
      techniques, 57–58
   and complexity of clinical studies, 50–51
   at core of agile clinical development, 263
   determining maximum safe drug doses, 60–67
   determining optimal drug doses, 69–75
   and future of clinical studies, 243–284
   increased interest in, 55–56
   issues with frequentist statistical method, 203–204
   look-ahead capabilities, 178
   maintaining integrity and validity, 48–49
   objections to methods, 47–51
   planning overview, 175–177
   planning tools and techniques, 182–196
   program advisory and oversight groups, 178–180
   regulatory environment, 50, 180
   role of contingency planning, 181
   role of external drug trial committees, 178–180
   types of design adaptations, 57–59
   value of early knowledge, 32–34
Adaptive Trials Simulator (software), 188
ADDPPLAN (software), 188
Advaria, 8
Agile clinical development
   adaptive research at core, 263
background, 145–146
data analysis tools as platform component, 236–237
data capture as platform component, 224–235
data cleaning and validation technology as platform component, 235–236
design considerations, 149–151, 157, 164–165
eight-point program, 284
essential types of data, 220–221
examples, 146–171
financial implications, 257–261
first steps, 262–264
five principles, 34–47
and future of clinical studies, 243–264
necessary infrastructure, 219–221
operational considerations, 152, 159–160, 160
phase I, safety, 149–156
phase II, efficacy, 157–164
phase III, confirmatory testing, 164–171
planning, 152, 158–159, 160–166
platform, defined, 224
randomization scheme as platform component, 237–238
site management as platform component, 238
supply-chain management as platform component, 239
time and cost savings, 155, 255–256, 257, 258–260
timeline comparison, 256
website as platform component, 240
Aitken, Murray, 8–9
Allman, Drew, 16
Alzheimer’s treatments, 11, 19, 128, 129
Anticoagulants, 4
Antidepressants, 11, 16
ARAND (software), 189
Armitage, P., 58
Atherosclerosis, 4, 88–89
Atorvastatin, 4
Auto industry, comparison of drug industry to, 41–44, 51, 246, 256, xiii
Avastin, 14
Azithromycin, 88–89
B
Backflow, 42, 44–48
Bauer, P., 56
Bayarri, M.J., 215
Bayesian statistical approach
in adaptive randomization, 103
applying to real world, 207–208
background, 204–205
compared with frequentist approach, 199, 208–212, 215
how it works, 206–207
regulatory considerations, 55, 56, 213–214
reliance of dose-finding methods on, 62, 63, 66, 74–75
role of prior distributions, 205–206, 210–212
using in clinical research, 208, 211–212
Berger, J.O., 215
Bidil, A-HeFT study, 86–87
Big Oil, comparison of drug industry to, 15–16
Big Pharma. See Pharmaceutical industry
Big Three U.S. automakers, comparison of drug industry to, 246, xiii
Big Tobacco, comparison of drug industry to, 15–16
Biologics, 5, 10, 12, 16–18
Biotechnology companies, 1–4, 5, 11, 12, 16, 17, 18, 20, 247, 248, 249–250
C
Cancer immunotherapy, 253. See also Oncology drugs
Case Report Forms (CRFs). See also Data capture
as backflow issue, 44–45
problems with, 37, 39, 44–45, 127, 128, 135
role in clinical research, 36, 44
role of electronic tools, 134–135
unprocessed, 44–45
Casper, Charlie, 189
Chien, Kenneth, 18
Chemotherapeutic agents
combination regimen for patients with acute myeloid leukemia, 104–105
combining in seamless phase II/II study, 92–93
China, 18, 19–21
Chronic kidney disease (CKD), 126
ClinBay, 188
Clinical studies. See also Agile clinical development
adaptive solution example, 1–4
agile, five principles, 34–47
application of lean approach, 42–43, 44, 45
average drug development time, 24
Bayesian statistics in, 208, 211–212
benefits of agile development, 146, 171–173
communications, 139–141
complexities of drug development, 5–6, 10–15, 21, 22–25, 50–51, 252
corresponding with frequentist statistical approach, 200–203
costs of conducting offshore, 19, 20–21
costs of conversion to efficiency, 29–32
data quality issues, 127–130
data base lock, 3, 130–136, 169, 170
future, 243–264
impact of individualization of medicine on, 253–254
importance of integrity and validity, 48–49
monitoring effort, 130–135, 159–160, 166, 166–169
objections to adoption of adaptive methods, 47–51
oncology drugs, 1–2, 11, 14, 19, 108, 130–131
optimizing enrollment, 119–127
regulatory environment, 50
resemblance to car manufacturing, 43–44, 51
role of query process, 43–44
role of technology, 46–47
screen failures, 33, 38, 121, 122, 125, 126, 161
site closeout, 130–136
site selection and management, 116, 118–119, 238
supporting functions, 139–142
uncertainties in research, 186
value of early knowledge, 32–34
Clinical Trial Management System (CTMS), 239
Combining drug trial phases. See Seamless drug trials
Confirmatory testing. See Phase III (confirmatory testing), agile clinical development
Contingency planning, in adaptive programs, 153, 181
Continual Reassessment Method (CRM), 62–66, 151, 154, 189
Contract Research Organizations (CROs)
adaptive solution proposal in troubled oncology study, 2–4
differences in STD treatment studies, 124–125
questions about sample size for clinical studies, 1–2
relationship to drug industry, 251–252
role in clinical research, 251–252
Covariate-adaptive randomization, 101, 102
CRFs. See Case Report Forms (CRFs)
Critical Path Initiative, FDA, 55, 186
CRM (Continual Reassessment Method), 62–66, 151, 154, 189
CROs. See Contract Research Organizations (CROs)
CTMS (Clinical Trial Management System), 239
CTriSoft, 188
Cytel, 187, 188

D
Danzon, Patricia, 17
Data analysis tools, 236–237
Data capture background, 224–225
comparative strengths and weaknesses of technologies, 226–227, 233, 234–235
digital pens for, 226, 227, 230–232, 234
feedback systems for, 229–230, 234
first generation technology, 227
interactive voice response systems for, 219, 230
PDAs and handheld computers for, 226, 227, 233
second generation technology, 227–230
selecting approach, 225
tablet PCs for, 226, 227, 232, 234
third generation technology, 230–235
using pen and paper, 227, 234
web-based systems for, 226, 227–229, 234

Data cleaning and validation, 235–236
Data quality. See also Performance metrics forms and instructions, 127
improving precision, 129–130
managing, 127–128
role of electronic tools, 134–135
site issues, 128–129
tracking incoming data, 128, 161-162
Data queries
and backflow, 45
data quality issues, 36, 37, 127-129
monitoring issues, 130-135
operational issues, 160-162, 165, 168-169
resolution, 118, 231-232, 234, 235, 236, 237, 249
role in clinical research, 43-44
and site management, 238
timely tracking, 36-39
Database lock, 3, 130-138, 169, 170
Decision maker (software), 188
Decision making
data acquisition for, 224-235
data cleaning and validation for, 235-236
time imperative, 40-41
tools for data analysis, 236-238
Decision trees
for deciding on sample-size reestimation, 182-185
as starting point for creating simulations, 195
Design adaptations
adaptive hypotheses and subpopulation analysis, 167-198
background, 56-57
in clinical studies to determine maximum safe dose, 56-67
in clinical studies to determine optimal dose, 67-75
compared with operational adaptations, 113-115
dependence on operational adaptations, 224
determining requirements, 176
infrastructure for, 113-114
management cycle for, 221-222
noninferiority-to-superiority design, 106
planning, 175, 176
as promising approach to cost-effectiveness, 248
types, 57-59
using randomization, 101-105
using sample-size reestimation, 80-89
using seamless studies, 89-100
value of early knowledge, 33

Dose-finding studies. See Phase II (efficacy), agile clinical development
Dose-limiting toxicity (DLT), 60, 62-66
DoseSim (software), 188
Dosing studies
background, 58-59
determining maximum safe dose, 59-67
determining optimal dose, 67-75
minimizing costs, 72-73
nomenclature, 58-59
phase I, safety, 59-67, 92-93, 139-150, 256, 257, 258-259
phase III, confirmatory testing, 67, 69-69,
70, 72, 73, 75, 99-100, 164-171, 256, 257, 258-260
Dr. Reddy's (Indian drug company), 20
Drucker, Peter, 35, 40, 262
Drug companies. See Pharmaceutical industry
Drugs. See also Clinical studies;
Pharmaceutical industry
cost issues, 14, 15, 21-22
oncology, 1-2, 11, 14, 19, 108, 139-131
statins, 4, 6-7
Durham, S.D., 56

E
East5 (software), 187
Eflulizumab, 104
Efficacy. See Phase II (efficacy), agile clinical development
Electronic data capture (EDC) systems, 228, 229-239, 244
Electronic medical records, 135, 232, 255
Elk Lilly, 9, 18, 252
Enrollment. See Adaptive enrollment
Erbitux, 14
European Medicines Agency (EMA), 50, 55, 213
ExpDesign Studio (software), 188
External committees, 178-179

F
Faxback systems, 229-230, 234
FDA (U.S. Food and Drug Administration)
average drug approval time, 24
and clinical trial efficiency issue, 50, 55, 185, 187, 213
Critical Path Initiative, 55, 185
and offshore drug companies, 19
Field monitoring, 39, 135, 138, 153, 160
Finkelstein, Stan, 22
Fisher, L, 62
Ford, Henry, 251
Forecasting drug-supply requirements, 194–196
FORTRAN (software), 189
Frequentist statistical approach
background, 199–200
compared with Bayesian approach, 199, 208–212, 215
cconcerns in clinical studies, 200–203
greatest strength, 214–215
issues with adaptive studies, 203–204

G
Garrett-Meyer, E., 64
GCP (Good Clinical Practice), 20, 134
Gemcitabine, 92–93
General Motors, 41, 246, 256
Genetic targeting, 16–18, 254
GlaxoSmithKline, 18
Globalization, 18–21, 249, 250–252
Good Clinical Practice (GCP), 20, 134
Goodman, S., 85
Group-sequential techniques, compared with
adaptative techniques, 57–58

H
Handheld computers (HHICs). See PDAs
(personal digital assistants)
Health-care system
and cost of drugs, 14, 15, 21–22
and public view of drug companies, 15–16
Herpes zoster, 33
Hill, A. Bradford, 47
HIV, 4, xii
Honda, 256

I
Ibuprofen vs. lumiracoxib, 88
idbounds (software), 189
Imatinib, 65–66
IMS Health, 8–9, 10, 21
India, 18, 19–21
Individualized medicine, 17, 21, 214, 243,
248, 253–254, 263
Infrastructure
for agile clinical development, 219–221
for design and operational adaptations, 113–114
special, for adaptive randomization, 103
Insulin sensitizers, 4
Interactive voice response system (IVRS), 219, 230
IRR (Internal Rate of Return), 257–258, 259
J
Jennison, Christopher, 57, 189
Johns Hopkins University, 169, 213
K
Köhne, K., 56
L
Lab results, assessing, 140–141
Lachin, J., 104
Lean thinking, 42–43, 44, 45, 262
Leukemia, 14, 104–105
Lipitor, 4, 8–7, 8
Little, R.J.A., 215
Lumiracoxib vs. ibuprofen, 88
Lupus, 97–98
M
Market capitalization, pharmaceutical industry, 8–9
M.D. Anderson Cancer Center, 189
Measuring productivity, 35–39
Media companies, 247
Medical records, electronic, 135, 232, 255
Merck, 7, 9, 33
Monitoring. See Adaptive monitoring
Myocardial infarction, 4, 89, 103–104
N
Neyman, J., 201
Nicholson, Sean, 17
Noninferiority-to-superiority design in test
drug studies, 105
Non-Q-wave myocardial infarction patient study, 103–104
Novartis, 18
NPV (Net Present Value), 258–260
Nuisance parameters, 80–81, 84
O
Offshoring, 19–21, 249, 250, 251, 252, 263
Ohno, Taiichi, 41, 42
Oncology drugs
case study, advanced/metastatic product, 108
clinical studies, 1–2
conducting clinical studies offshore, 19
example of monitoring effort, 130–131
lengthening developmental timeline, 11
prohibitive cost, 14
O’Neill, Robert, 187
Operational adaptations
benefits, 115
compared with design adaptations, 113–115
data quality as issue, 127–130
defined, 113
dependence of design adaptations on, 224
determining requirements, 177
enrollment as issue, 116, 117, 119–127
implementing, 116–142
infrastructure for, 113–114
list of rules, 141
management cycle for, 221, 223
meeting requirements, 177
monitoring as issue, 130–135, 159–160, 166, 168–169, 223, 249
nature and significance, 115
planning, 175–176, 177
problems with current operational
approach, 115–116
promising approach to cost-effectiveness, 248–249
site selection and management, 116, 117, 118–119, 136–138
Optimal (software), 189
Optimal dose selection, 67–75
O’Quigley, J., C., 62
Orphan Drug Act, 4
Outsourcing, 18, 21, 251–252

P
Pancreatic cancer, 92–93
Patent cliff, defined, 6
Patent exclusivity, 8–7
Patient recruitment. See Adaptive enrollment
PDAs (personal digital assistants), 226, 227, 233
Pearson, Egon, 201
Pepe, M., 62
Perez, Oscar A., 189
Performance metrics, 35–40, 220–221, 223.
See also Data quality
Personalized medicine. See Individualized medicine
PEST (software), 189
Pfizer
Chinese operations, 18
and Lipitor, 4, 6–7
market capitalization, 9
and patent cliff, 8
and Zithromax, 89
Pharmaceutical industry
average drug development time, 24
comparison to automobile industry, 41–44, 51, 246, 256, xii
comparison to industrial partials, 15–16
competition from biotechs and small
companies, 17–18, 249, 250
competition from generics, 8–9
current business challenges, 6–10
declining revenues, 8–9
in developing countries, 19–21, 247, 249
drug development cost issues, 5–6, 15–21, 22, 260–261
drug development failures, 6–7
history of industrial success, 4
impact of globalization, 18–21
impact of increasing drug prices, 12, 14–15
inefficiencies in new drug development, 5–6, 21
interest in adaptive methods, 55–56, 269–261
need for change, 247–248
public view of drug companies, 15–16
relationship of drug companies to CROs, 251–252
Phase I (safety), agile clinical development
background, 59–67
benefits realized, 154–155
combining with phase II, 92–93
design considerations, 149–151
estimated cost savings, 257, 258–260
executing plans, 153–154
operational considerations, 152
planning, 152
scenario, 149–158
timeline comparison, 256
transition from phase I to phase II, 156
Phase II (efficacy), agile clinical development
background, 58–59, 67–75
benefits realized, 163
combining with phase III, 96–98
design considerations, 157
estimated cost savings, 257, 258–260
executing plans, 160–163
operational considerations, 159–160
planning, 158–159
sample-size reestimation, 162
scenario, 157–184
INDEX

timeline comparison, 256
transition from phase II to phase III, 164
Phase III (confirmatory testing), agile clinical development
  background, 67, 68–69, 70, 72, 73, 75
  benefits realized, 169–170
  combining with phases I and II, 98–100
design considerations, 164–165
  estimated cost savings, 257, 258–260
  executing plans, 167–169
  operational considerations, 166
  planning, 165–166
  sample-size estimation, 167
scenario, 164–171
timeline comparison, 256
transition from phase III to regulatory filings, 171
PhRMA. See Pharmaceutical industry
Plantaddis, S., 64, 65
Plavix, 8
Pocock, S., 56, 103
Postmarketing studies, 254–255
Predictive Probability (software), 189
Proof of concept (PoC) studies, 67, 74, 157
Protocol amendments, 32
Pruning. See Optimal dose selection
Psoriasis, 85–90
S
  Safety. See Phase I (safety), agile clinical development
Salsburg, David, 200
Samarium-153, 64–65
Sample-size reestimation (SSRE)
  adjusting for observed treatment effect, 86–89
  background, 3, 80
  benefits, 82
case studies, 1–4, 85–89
  in confirmatory phase of agile clinical development, 167
  in efficacy phase of agile clinical development, 162
  initial sample size determinants, 80–81
  nuisance parameter adjustments, 80–81, 84
  operational considerations, 85–86
  preserving statistical validity, 83
  restrictions, 84
  role of decision tree in deciding on, 182–185
  value of early knowledge, 32–33
SAS (software), 189
Scientific management, 35
Screening programs, 253
Seamless drug trials
  background, 89–90
  combining phases I, II, and III, 98–100
  combining phases I and II, 66–67, 92–93
  combining phases II and III, 93–98
  planning issues, 95–96
  role of between-phase pauses, 69–90
timeline comparison with conventional trials, 98, 99
when to consider, 90–91
SFT (Supply Forecasting Tool), 188
Simon, R., 103
Simulations
  applications in clinical research, 186–187
  background, 190
  benefits, 190
  and clinical research uncertainties, 186
  compared with decision trees, 185–186.
  defined, 185
  forecasting drug supply requirements, 194–196
  limitations, 193–194
  list of tools, 187–189

R
R Project (software), 189
Ranbaxy Laboratory, 6, 20
Randomization. See Adaptive randomization Recombinant proteins, 16, 97–98
Recruitment. See Adaptive enrollment Regulatory considerations
  impact of adaptive programs on approval process, 180, 254
  interest in adaptive methods, 50, 180
  and postmarketing studies for new drug products, 254–255
  reception for Bayesian statistical approach, 55, 56, 213–214
  role in clinical studies, 50
  transition from phase III to filings, 171
Research. See Adaptive research; Clinical studies Response-adaptive randomization, 102, 104–105
Rework, 36, 38, 42, 43–44, 146
Roche, 18
sample-size determination example, 193–194
step by step, 190
steps involved in conducting clinical studies, 185–196
study planning tool, 190–192
Simvastatin, 7
Site closeout, 136–138
Site selection and management, 116, 118–119, 158, 159, 238
Source data, defined, 134
SSRE. See Sample-size reestimation (SSRE)
Statin, 4, 6–7
Statistics
Bayesian approach, 199, 204–208
comparing frequentist and Bayesian approaches, 199, 208–212, 215
frequentist approach, 199–204
STD (sexually transmitted disease) study adjusting enrollment strategy, 33–34
improving slow enrollment, 124–125
Streptomycin, 47
Stroke, 66, 95–97
Sun Pharma, 20
Supply-chain management, 141–142, 239–240, 247, 251
Surrogates, 68, 73, 147, 149, 157, 164
T
Tablet PCs, 225, 227, 232, 234
Taylor, Frederick, 35
TCVVisualize (software), 188
Technology
and basic monitoring tasks, 134–135
for data capture, 225–235
for data cleaning and validation, 235–236
redefining work processes, 135
role in clinical studies, 46–47
Tamin, Peter, 22
Tessella/Derry, 188
Top-down management approach, 39–40
Torcetrapib, 6
Tourettes, 188
Toyota, 41–42, 46, 246, 251
TPA (tissue plasminogen activator), 66–67
Treatment switching, 109
Treatment-adaptive randomization, 101, 102
Turang, Alan, 207
Turnbull, B.W., 57

U
University of Reading, 180
Urn-adaptive biased-coin randomization method, 104–105

V
VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital) trial, 103–104
Viagra, 8

W
Wald, A., 56
WalMart, 247
Warner Lambert, 6
Web-based EDC (electronic data capture) systems, 226, 227–229, 234
Websites, creating for clinical studies, 139–140, 240
Wel, L.J., 56, 104
WIZARD (Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders), 89
Womack, James, 42
Wyeth, 6–7, 9, 251

Z
Zahurak, M., 65
Zelen, M., 56
Zevalin, 14
Zithromax, 88–99
Zocor, 7
Zostavax, 33