INDEX

3+3 design, 220
α (notation), 769
α level, 560
α spending, 564
χ (notation), 770
δ (notation), 769
e (notation), 769
γ (notation), 769
λ (notation), 769
μ (notation), 769
ν (notation), 769
Ω (notation), 770
ϕ (notation), 769, 770
π (notation), 769
Π (notation), 769
ρ (notation), 769
σ (notation), 769
Σ (notation), 769
τ (notation), 769
def. (rate), 771
estimating, 264
number of events, 265
low, 264
modeling, 265
power, 469
quantitative estimates, 265
run-in period, 264
accurate
def., 771
active control, 772
active sampling, 258, 271
adaptive design, 413, 415
barriers, 428
case study, 428
adaptive randomization, 418, 423, 503
adherence, 106, 482, 576
def., 771
adjusted analyses, 214, 662
def. of adjustment, 772
example, 664
reporting, 724
advocacy, 79
AIDS, 166, 186, 658
advocacy, 79

abbreviations, 763, 764, 766, 767
absolute risk reduction, 150
accountability, 736
accrual
   assessing, 264
trials, 20
  prognostic risk group analysis, 657
allocation ratio, 460
  power, 469
alpha error
  def., 772
alternative hypothesis, 179, 382
Alzheimer’s Disease Anti-Inflammatory
  Prevention Trial, 104
American Association for Thoracic Surgery, 128
American Statistical Association, 85
code of conduct, 84
amrubicin, 386
analysis, 219
  adjusted, 661
  based on adherence, 576
  basis of, 590
covariance, 610
  preplanned, 592
  prognostic factors, 644
  treatment received, 578
antiplatelet therapy
treatment analysis, 704
area under the curve, 349, 438, 578, 594, 596, 597, 720
  def., 772
aripiprazole, 409
assessment bias, 184
auditing, 756
authoritarianism, 183
authorship, 726
governance, 730
  inclusion and ordering, 726
  models, 728
  responsibilities, 727
autonomy, 25, 63
  def., 772
AZT. see zidovudine

B (notation), 769
Babbage, C., 734
background information, 248
balanced design, 504
  def., 772
barriers to participation, 268
baseline, 772
basket trial, 407
  def., 772
Bayesian methods, 198, 199, 204, 349, 417, 447, 523
  Bayesian versus frequentist inference, 208
  confidence interval, 446
  data-dependent stopping, 545, 556
  example, 557
difficulties, 206
dose-finding, 337
eexample, 206
  inference, 205
  posterior distribution, 208
SA trials, 447
Bayes rule, 287, 379
Bayes theorem, 179, 207
  def., 772
BCNU, 664
Belmont Report, 62, 740
beneficence, 64
  def., 772
Benford’s law, 736
Bernard, C., 19
beta distribution, 259
beta error
  def., 772
betting, 592
bias, 31, 172, 173, 219, 223, 492
  assessment, 184
  biased randomization, 505
  clinical, 181
  confirmation, 184
  control, 187, 399
  def., 772
dose-ranging designs, 343
  early stopping, 188, 189, 565
  estimation, 192
  in incompletely specified models, 655
  meta-analysis, 700
  publication, 182, 713
  selection, 121, 182, 713
  size, 181
  sources, 182
  staged designs, 189
  statistical, 188
  structural, 185
  survivor, 189
  versus random error, 172
binary variable
  def., 773
binomial distribution
  def., 773
bioassay, 336
biological determinism, 280
biologicals, 101
biomarker, 402, 423
  enrichment, 403
  middle development, 375
  multiple, 405
  predictive, 403
  prognostic, 403
  prospective-retrospective, 406
types, 402
  validation, 403
biomarker strategy design, 404
biomarker stratified design, 404
blinding. see masking
INDEX 873

block
def., 773
blocked randomization
def., 773
blocking, 234, 500, 501, 503
  maximum imbalance, 501
  proper analysis, 503
  size, 503
  variable size, 501
bloodletting, 19
bupivacaine, 350
B-values, 568
calibration, 139
Cancer and Leukemia Group B, 633
cancer trials, 20
capacity
  for informed consent, 68
captopril, 169
cardiac arrhythmia suppression trial, 169
cardiovascular disease trials, 20
case-control design, 39
case-control study, 18
case report, 226
def., 773
series of, 226
case series, 122, 226
def., 773
causal
def., 773
causality, 40
cavia porcellus, 26
censoring, 155, 156, 588, 601
  administrative, 158
  competing risks, 159
def., 773
  dependent, 154, 159
  independent, 156
  informative, 156
  interval, 156
  left, 156
  right, 156
time to good outcomes, 160
  type I, 156
  type II, 156
  type III, 156
  vs loss to follow-up, 157
Center for Health Care Technology Assessment, 126
Center for Medicare and Medicaid Services, 88, 125
central review, 161
Christmas tree design, 561
cinnamon, 109
classification, 142
clinical alerts, 731
clinical reasoning, 14, 15
clinical research
  spectrum of, 28
    including trials, 28
clinical significance, 142, 607
clinical trial
  application, 31
  in complementary and alternative medicine, 107, 108
  complexity, 219
  contexts, 87
def., 21, 773, 785
devices, 96
  context, 95
  DF, 304
dose-finding (DF) trials, 304
drawbacks, 30
  of drugs, 90
  context, 93
  ethics, 43
  expanded safety (ES) trials, 401
Hippocratic oath, 53
history, 19, 20
large-scale (LS), 400
phase I. see treatment mechanism (TM) or dose finding (DF)
phase II 372. see also SA
phase III 7. see also comparative trial
phase IV 401. see also expanded safety (ES)
populist view, 24, 50, 90
predicates, 29
protocols, 243
purpose, 223
as a research design, 10
risk, 50
  safety and efficacy (SA) trials, 371
  small, 33
  in surgery, 116, 118
  TM, 304
treatment mechanism (TM) trials, 304
types, 7
  use of, 87
clinical utility
  efficacy and toxicity, 363
cluster randomization, 409, 481
Cochrane Collaboration, 89
coding of variables, 648
coenzyme Q, 386, 388, 392
coenzyme Q10, 388, 428
  cognitive impairment, 147
  cohort
def., 773
  cohort design, 39
  cohort heterogeneity, 392
COMMIT trial, 232
common sense, 36
community intervention trials, 232
companion diagnostics, 280
comparative treatment efficacy (CTE) trial
def., 774
comparative trial, 372, 397
adjuvant, 400
bias, 185
biomarkers, 402
choosing \( \alpha \) and \( \beta \), 459
equivalence, 401
multiple institutions, 399
pivotal, 400
power, 457
replicated, 398
reporting, 721
single modality, 400
compassionate use, 50
competing risks, 159
complementary and alternative medicine
characteristics, 112
def., 107, 108
rigorous evaluation, 113
use of trials in, 111
complexity, 397
compliance monitoring, 264
composite outcomes, 154
PFS, 159
comprehension
for informed consent, 68
computer software
frequentist stopping boundaries, 570
concept sheet, 244
conditional power, 566
confidence interval, 176, 205, 439
Bayesian, 446
def., 774
event rate, 451
exact binomial, 441
mean, 438
confirmation bias, 295
confirmatory trials, 29
conflict of interest, 83, 84, 297
conflicts of obligation, 47
confounder, 492
def., 774
confounding by indication, 645
consent, 68
CONSORT statement, 709
constant infusion, 597
constraints, 218
contexts, 87
complementary and alternative medicine, 107
devices, 95
diagnostic trials, 134
drugs, 90
overview, 90
prevention, 99
radiotherapy, 134
screening, 129
surgery, 116
continual reassessment method, 344, 345
equivalence, 401
example, 346
pharmacokinetic measurements, 348
for two interacting drugs, 360
continuous
def., 774
controls
concurrent, 186
historical, 38
convenience sampling, 271
Coronary Drug Project, 576
correct ordering, 390
correlation coefficient
def., 774
z-transformation, 34
cost, 397
cost optimization, 481
covariates, 644, 661
correlated, 654
models for, 648
time dependent, 646
creatinine, 384
credible interval, 449
critical value, 175
crossover trial, 684
advantages and disadvantages, 686
analysis, 689, 691, 695
applications, 690
carryover, 689
effects, 688
correlations, 687
def., 684, 774
dropouts, 689
example, 696
factorial, 685
limitations, 686
linear model, 692
multiple treatments, 685
precision, 687
prerequisites, 689
recruitment, 687, 688
test of carry over effect, 692
treatment by period interaction, 692
two-stage analysis, 691
variance of treatment effect estimate, 687
washout period, 690
cross sectional study, 39
cytomegalovirus, 37
cytoxan, 607
Dalton, 734
Darsee, J.R., 747
INDEX 875

data, 761
def., 774
databases, 39, 227
data-dependent stopping, 522, 777
  approaches to evaluating evidence, 544
def., 774
DSMC review, 541
frequentist methods, 560
group sequential, 559, 561
likelihood methods, 551
pros and cons, 526
reasons, 524
SA trials, 455
sequential methods, 560
statistical guidelines, 545
tension, 525
data imperfections, 573, 582
data management
  protocols, 251
data torturing, 629
decision theory, 198
data-dependent stopping, 546, 559
demonstration trials, 78, 242
design
  assumptions
  Bayesian, 205
  benefits from, 220
  blocking, 234
  comparative trials, 227
  components, 228
  concepts, 225
def., 21
  error control, 228
  essentials, 223
  ethics, 74
  experimental units, 232
  factors, 233
  flaws, 219
  foundations, 226
  goals, 223
  hybrid, 242
  importance, 219
  limitations, 242
  measurement, 143
  monitoring, 538
  NETT, 126
  non-experimental, 37
  observational units, 232
  phase I trials, 333, 337
  randomization, 233
  sampling, 228
  simplicity, 224
  surgical trials, 116, 120, 122
  treatment, 228
  types of trials, 7
designed data production, 15, 17
determinism
  def., 774
deterministic
  def., 774
development design, 279
development paradigm, 277
developmental pipeline, 281, 417
device, 95
  development, 97
  safety, 97
device regulation, 95
device trials, 96
  device function versus clinical outcome, 253
diagnostic trials, 134, 218
dichotomous
  def., 775
dimethyl sulfoxide (DMSO), 73
disbelief, 296
disease free survival, 159
disease modification, 144
DMSO, 73
dopamine, 123
dosage modifications, 249
dose
  versus efficacy, 385
dose finding, 184, 329, 333, 345, 418, 437
dose finding trial (DF), 333
  bias, 184
def., 775
  dose-limiting toxicity, 339
dose optimality, 335
dose-ranging, 333
dose-response, 354
  logistic model, 337
dose-response model, 361
double masking, 186
doxorubicin, 607
drop-in
  def., 775
dropout
  def., 775
drug context
  vs device context, 97
drug distribution, 594
drug information, 249
dual dose-finding, 358
duality, 45, 47, 54
duct tape, 109
due process (in misconduct), 746
dynamic balancing, 420

early stopping, 522
Ebola, 102
ECMO, 30, 76, 506, 519, 526
E. coli, 56
economics, 242
effectiveness
INDEX

def., 775  
method, 575  
versus efficacy, 269, 574  
effect size, 11  
efficacy, 579  
def., 775  
versus effectiveness, 269  
eligibility  
criteria, 254, 256, 269, 415, 540, 580  
def., 775  
errors, 580, 581  
protocol, 249  
reporting failures, 722  
emphysema, 88, 124  
empiricism, 22  
encainide, 169  
endpoint, 144, 590  
ascertainment, 187  
def., 775  
dichotomous, 463  
hazard ratios, 464  
enrichment, 188, 230, 392, 393, 403, 424  
enthusiastic prior, 558  
entropy, 320  
bias, 321  
empirical variance, 322, 323  
epidemiologic studies, 227  
equipoise, 45  
equivalence trials, 401  
error  
control, 399  
random, 172  
random versus systematic, 138  
error control, 382, 387, 401  
estimate  
def., 775  
estimation, 141  
unbiased, 192  
ethics, 43  
abortion, 55  
autonomy, 63  
Belmont Report, 62  
beneficence, 64  
collaborative partnership, 66  
crossovers, 686  
data-dependent stopping, 522  
double standards, 49  
epidemiologic, 47  
examples of competing obligations, 54  
fair subject selection, 67  
favorable risk-benefit, 67  
Hippocratic oath, 52  
implications, 65, 72  
independent review, 68  
informed consent, 68  
international guidelines, 57, 61  
investigator competence, 65  
IRBs and TEMCs, 530  
IRBs, 62  
justice, 65  
lapses, 57  
managed care, 56  
organ donation, 55  
overview for trials, 44  
physician obligation, 47  
physician roles, 54  
practitioner lack of knowledge, 72  
principles, 63  
quarantine, 55  
questionable treatments, 73  
randomization, 44  
research versus practice, 48  
respect for subjects, 71  
scientific validity, 66  
scientific value, 66  
selection criteria, 257  
for the statistician, 84  
study design, 65, 66  
teaching and training, 54  
triage, 55  
trial design, 74  
vaccination, 55  
evaluability  
criteria, 581, 583  
def., 775  
event rate, 35  
cause specific, 587  
data-dependent stopping, 554  
events  
counting, 574  
uncounted, 587, 588  
event times, 155, 156, 160  
evidence, 1, 210, 299, 383, 434  
misleading, 434  
mistakes in evaluating, 293  
weak, 434  
EWOC, 344, 351  
exclusions, 183, 577  
criteria, 256, 262  
post hoc, 187  
reporting, 725  
expanded access, 51  
expanded safety (ES) trial, 478  
def., 775  
purposes, 401  
experiment, 15, 23, 27, 217  
characteristics, 27  
def., 21, 775  
experimental method, 19  
experimental unit  
def., 775  
experiment design, 11, 217, 218  
explanatory perspective, 574, 575
exponential distribution def., 775
ternal validity, 182, 224, 265
selection criteria, 263
factor, 671
def., 776
levels, 233, 671
factorial designs, 106, 671, 685
2 by 2 by 2 design, 672
2 by 2 design, 672
adaptive randomization, 420
advantages, 674
characteristics, 672
estimating interactions, 675
estimating main effects, 674
examples of trials, 680
incomplete, 682
interactions, 675, 677
and scale of measurement, 677
linear models, 678
main effects, 677
partial or fractional, 682
precision, 675
false negative, 383
false positive, 383
 falsifiability, 22
feasibility, 116, 331, 371
fialuridine, 310
Fibonacci, 339, 358
dose-ranging, 337, 344
ficainide, 169
flosequinan, 169
fluoride, 170
follow-up, 776
active versus passive, 187
losses, 587
Food and Drug Administration, 91
Food, Drug, and Cosmetic Act of 1938, 95
Frankenstein myth, 25
fraud, 84, 734, 737
frequentist methods, 198, 202, 560
inference, 208
futility, 381–384
design, 381
error control, 382
gain score, 610
Galen, 183
Galileo, 6, 734
Galton, Francis, 14
ganciclovir, 37
Gavarret, L.D.J., 19
gender representation, 270
generalization, 14
linear models, 649
gene therapy, 47
genomic determinism, 299
glaucoma, 166
golden ratio, 339
gout, 14
Greek letters, 769
group sequential designs
safety and activity (SA) trials, 456
guinea pig, 26
happenstance data, 12
harmonic mean hazards, 484
Hawthorne effect, 145
Haybittle–Peto boundary, 563
hazard, 149
estimate, 464
hazard function regression def., 777
hazard rate, 603
confidence intervals, 605
def., 776
hazard ratio, 149, 464, 561
confidence limits, 464
def., 777
power and sample size, 465
healthy worker effect, 122
Helsinki Declaration, 58, 61, 740
HER2, 12
Herceptin, 12
heterogeneity
two-way control, 234
hierarchy of evidence, 228
Hipparchus of Rhodes, 734
Hippocratic oath, 52
historical controls, 38
HIV, 37
Huntington’s Disease, 386
hydrazine sulfate, 24, 73, 114, 632, 634
hypothesis tests, 172, 174, 202, 203
one- or two-sided, 177
random error, 175
ICMJE, 89, 711
IEC, 68
ignorance, 108
imiparib, 386
imputation, 653
of missing values, 584
inclusion criteria
excessive, 262
inclusiveness, 267
incremental improvement, 14, 90, 119, 132
IND
investigator responsibilities, 758
sponsor responsibilities, 759
Independent Ethics Committee. see IEC
indicator variables, 648
ineligible subjects, 580
inference, 196
Bayesian, 204
def., 777
frequentist, 202
likelihood, 210
methods other than trials, 35
inferiority
threshold, 240
informed consent, 58, 63, 68, 268
common errors, 69
elements of, 69
in emergency settings, 70
Institutional Review Board, 62, 68, 81
integrity, 736
in research, 737
intention to treat, 148, 214, 540, 576, 577
def., 575, 777
interaction, 11, 18, 646, 655, 675, 676, 682, 688
in factorial designs, 675
representation, 273
treatment-covariate, 645
treatment by period, 688
interim analysis, 522
def., 777
interim selection, 423
intermediate outcomes, 167
International Conference on Harmonisation, 244
essential documents for a clinical trial, 244
trial reports, 715
International Statistical Institute, 84
interval scales, 142
investigator competence, 66
investigator responsibilities, 82, 757
ISIS-2, 526, 632
ivacaftor, 11
Jewish Chronic Diseases Hospital, 58
justice, 65
Laebrile, 51, 73, 230
large scale trials, 215, 255, 256, 269, 402
large simple trials, 400
last observation carried forward, 585
late failures, 292
latency, 221
Latin square, 234
Latrile, 114
Leibniz, 734
leuprolide, 165
lifetables, 485
likelihood, 199, 210, 434, 449, 462, 477, 480
def., 777
design, 211
event rate, 454
example, 211
function, 200, 207
monitoring methods, 551
ratio test, 552
sample size, 450, 462
support intervals, 211
linear model, 610
Linnaeus, 14
local control, 218
Local Research Ethics Committee, 68
logistic model, 65
logistic regression
def., 778
logrank statistic, 561
Long, J., 735
lost to follow-up, 588
def., 778
vs censoring, 157
Louis, P.C.A., 19
LS trials
def., 778
lung cancer, 607
lung volume reduction surgery, 40
see National Emphysema Treatment Trial
MACE, 154
masked
def., 778
masking, 186, 236
double, 186
masked monitoring, 532
triple, 186
master protocols, 407
def., 779
MATCH trial, 407
matrix
def., 779
maximum likelihood estimate, 201
maximum nontoxic dose, 335
maximum tolerated dose, 335
def., 779
drug combinations, 356
MCID, 717
mean
def., 779
mean squared error, 193
measurement, 137
def., 779
design, 137, 143, 153
efficiency, 153
error, 627
scales, 142
Mendel, G., 734
mentoring, 741
mesothelioma, 599
INDEX

879

meta-analysis, 215, 243, 698, 713
bias, 700
cumulative, 703
def., 779
element, 704
history, 698
limitations, 706
methods, 700
observed minus expected, 703
precision, 699
quality rating system, 703
reviews, 699
statistical analysis, 703
study eligibility criteria, 702
study retrieval, 701
method effectiveness, 575
middle development, 370, 371
characteristics, 372
choices, 375
constraints, 373
goals, 372
randomization, 377
skipping, 376
true positives, 379
milrinone, 169
minimally important difference, 179
minimization, 233, 504
minimum effective dose, 335
def., 779
minocycline, 384
minority representation, 270
misconduct, 734
basic sciences cases, 735
case histories, 747
causes, 742
clinical sciences cases, 735
confidentiality, 744
definition, 738
detecting, 755, 760
frequency, 741
fringe science, 734
German cases, 752
impact, 751, 752
importance in clinical sciences, 737
investigations
outside the U.S., 739
PHS policies, 743
PHS regulations, 743
Piltdown Man, 734
potential problem areas, 755, 756
prison time, 735
problem areas, 746
psychology, 743
recent, 735
recognizing, 754
role of ORI, 745
statistical sciences cases, 736
missing data, 584, 652
random, 585
mixtures, 392
models, 18, 197, 299, 626, 647, 648
building, 650
characteristics, 647
def., 779
generalized linear, 649
incomplete specification, 655
interactions, 655
logistic, 649
missing data, 652
multiple regression, 653
preclinical, 298
proportional hazards, 648
random effects, 650
risk groups, 656
monitoring, 527
Bayesian methods, 557
components, 524
def., 779
ethics, 77
motives, 523
report, 527
morinicine, 169
most likely to succeed dose, 335
MTD, 336
multiple comparisons
def., 779
multiple imputation, 586
multiple treatments, 218
multiplicity, 176, 629, 630
def., 780
multivariable
def., 780
multivariate
def., 780
National Death Index, 587
National Emphysema Treatment Trial, 40, 88,
122, 124, 243, 584, 718
results, 127
National Heart Lung and Blood Institute, 125
National Research Act of 1974, 62
negative findings, 714
reporting, 724
negative results, 716
nesting, 233
def., 780
models, 654
neural networks, 667
Newton, Isaac, 734
nifedipine, 707
NIH Revitalization Act of 1993, 270
non-experimental designs, 37, 38
non-inferiority, 410
non-superiority, 381
nonadherence, 579–581
power, 485
sample size inflation, 482
treatment, 575
noninferiority, 239
confidence limits, 474
likelihood, 477
sample size, 472
threshold, 240
nonuniformity of treatment effect, 231
nonvalidated practice, 47
norms of science, 738
North Central Cancer Treatment Group, 633
notation, 6, 768
Greek, 769
Roman letters, 770
NSABP, 748, 750, 752
null findings, 716
null hypothesis, 178, 382, 457
def., 780
null results, 714
number needed to treat, 150
Nuremberg Code, 57, 61, 787
Nuremberg trials, 57

O’Brien-Fleming boundary, 563
objectives, 140
internal, 140
protocol, 248
selection, 141
objectivity
in monitoring, 535
observation, 226
def., 780
model, 221
observational study
def., 780
observational unit
def., 780
observer bias, 90, 92, 121, 122
odds
def., 780
ratio, 149
def., 781
Office for Human Research Protections, 75
Office of Research Integrity, 741
open access publication, 731
operating characteristics, 422
dose-ranging designs, 340
pipeline, 286
optimal allocation, 411
optimal biological dose, 330, 335, 781
optimization
joint for safety and efficacy, 361
ordered categories, 147
ordering, 142
ORI, 745

ornithine transcarbamylase, 47
Osler, W., 225
outcomes, 146
censoring, 156
composite, 154
counts, 147
dichotomous, 148
evaluating, 144
event times, 155
hard, 145
intermediate, 167
measured values, 146
middle development, 374
ordered categories, 147
patient reported, 161
as predictors, 143
qualitative versus quantitative, 146
quality of life, 161
repeated measures, 160
research, 40
surrogate, see surrogate outcome
survival, 158
translational trials, 314
unordered categories, 148
overview, see meta-analysis
def., 781

paradigm, 282
parallel design
def., 781
parameter, 197, 647
def., 782
Parkinson’s disease, 98, 123, 384
partial sums, 566
patient reported outcome, 138, 161
PD-1, 12
PD-L1, 12
peer review, 712, 755
pembrolizumab, 427
penalized likelihood, 193
permutations
number of, 510
test, 509
element, 511
personal care principle, 51
personalized medicine, 11
pharmacokinetic model, 348, 591, 594, 595, 598
reporting, 720
phase I, 333
phase I trial, 7, 329
def., 782
designs in use, 337
healthy volunteers, 353
ideal design, 336
MTD, 353
objectives, 141
purposes, 333
reporting, 719
phase II trial, 7
def., 782
phase III trial, 7
def., 782
phase IV trial, 7
def., 782
physician behavior
trial reports, 710
Physician Data Query, 88
Physicians’ Health Study, 680
Piltdown Man, 734
pipeline
definition, 277
implications, 291
optimistic, 283
optimization, 288
phases, 278
problems, 281, 286
properties, 370
quantitative, 286
skeptical, 284
and study design, 283
pivotal trials, 400
placebo, 59, 78, 90, 92, 119, 237
def., 782
effect, 10, 15, 117, 186, 238
experimental, 237
surgical, 117, 122
use of, 239
platform trial
def., 782
platinum, 607
play the winner, 419, 505
Pocock boundary, 563
Poisson distribution, 478
Poisson rates, 479
Poisson, R., 748
polio, 20, 55
polyposis, 607, 609
portacaval shunt, 121
posterior distribution, 207
postmarketing surveillance, 401
power, 179, 222, 430, 432, 463, 464
calculating, 435
comparative trials, 457
computer programs, 487
curve, 179, 488
def., 782
equivalence trials, 239
event rates, 464
nonparametric assumptions, 466
nonadherence, 484
parametric assumptions, 464
post hoc, 180

for prognostic factor analyses, 660
sample size, 435
simulation, 487
t-test, 459
practice
vs research, 48
pragmatic perspective, 574, 575
precise
def., 782
precision, 219, 223, 432, 439, 609
def., 782
direct specification, 432
medicine, 11
def., 782
relative, 453
prevention, 10
primary, 99, 103
secondary, 99
tertiary, 99
prevention trials, 99, 100, 218
error rates, 459
methodology, 105
vs therapeutic trials, 100
primary outcome, 782
prior distribution, 205, 447, 557
clinical, 206
eliciting, 206
enthusiastic, 206
reference, 206
skeptical, 206
privacy, 71
probit
def., 782
problems with trials, 284
product limit method, 157, 602, 603
professional conduct, 83
prognostic biomarker, 403
prognostic factor, 403, 600, 626
analysis, 644
balance, 499, 501
characteristics, 646
control, 499
def., 782
motivations, 645
neural networks, 667
nonmodel methods, 665
recursive partitioning, 666
sample size, 486
scale of measurement, 648
prognostic factor analysis
power and sample size, 660
progression, 159
free survival, 159
proportional hazards
def., 782
model, 648
proportions, 34
prostatectomy
  robotic, 45
protocol, 243, 542
  agent information, 249
  background information, 248
  concept sheet, 244
  def., 783
deviation, 245
deviations, 245
dosage modifications/side effects, 249
drug information, 249
eligibility criteria, 249
importance, 243
objectives, 248
outline, 246
publishing, 714
purposes, 244
randomization, 249
serial measurements/study calendar, 248
staking criteria, 248
statistical section, 250
treatment evaluation, 250
treatment program, 248
PSA, 163, 165, 402
pseudorandom numbers, 508
def., 783
Ptolemy, 734
publication bias, 30, 182, 297, 713
def., 783
p-value, 178, 204
def., 783
early stopping, 563
meaning, 178
poor properties, 619
reporting, 717, 725
statistical significance, 609
strength of evidence, 174
summarizing data, 176
type I error, 178
versus confidence intervals, 619
quality assurance
  DSMC, 540
quality of life, 138, 161
quantile
def., 783
quinine, 115
radiotherapy, 111, 134
random
  def., 783
  effects models, 628
random error, 172, 173, 217
  size, 181
  versus bias, 172
random missingness, 585
randomization, 19, 21, 32, 214, 218, 304, 353, 378, 494, 690
  adaptive, 503
  administration, 507
  benefits of, 497
  bias control, 185
  blocked, 500
  causal inference, 495
  cluster, 481
  clusters, 495
  constrained, 500
  control over unknown factors, 497
  control over, 498
  in crossover trials, 686
def., 783
design, 233
difficulties with, 32
discontinuation of a subset, 126
ethics, 44, 76
failed, 518
from the first patient, 32
imbalances, 498
justification of type I errors, 509
in middle development, 291, 386, 389
need for, 493
pre-randomization, 519
protocol, 249
reasons for early initiation, 32
safety and activity trials, 378, 389
sealed envelopes, 508
simple, 498
tests, 509
treatment mechanism trials, 304, 353
tuberculosis trial, 494
unbalanced, 76
urn designs, 504
randomized discontinuation, 241
randomized phase II, 387
randomized trials
  key features, 399
  true positive rate, 398
ranking and selection designs, 391
rate
def., 783
total
  def., 783
  scales, 142
rationalism, 22
RCT, 397
  key features, 399
  reliability, 398
reasoning
  clinical, 14, 17
  statistical, 15–17
recursive partitioning, 666, 667
re-design, 425
registration of trials, 88, 89, 711
regression model
collinearity, 654
multiple, def., 780
multivariable, 653
univariable, 653
regression to the mean, 237
relative risk, 149
reliability
of RCTs, 398
repeated measures, 160
replication, 173, 218, 231
reporting, 709
abstracts, 711, 718
structured, 719
biological consistency, 725
comparative efficacy trial background, 722
comparative efficacy trial discussion, 724
comparative efficacy trial figures and tables, 725
comparative efficacy trial methods, 722
comparative efficacy trial results, 723
CONSORT, 709
efficacy, 720
electronic, 730
eligibility failures, 722
epidemiologic studies, 710
evaluating the literature, 712
exploratory analyses, 725
guidelines, 709
ICH, 709
guidelines, 715
ICMJE, 709
intention to treat, 725
negative results, 714
objectives of phase I trials, 719
patient characteristics, 720
peer review, 712
pharmacokinetic models, 720
phase I trials, 712, 719
publication bias, 713
p-values, 725
safety and activity event rates, 721
safety and activity feasibility, 721
safety and activity treatment comparisons, 721
safety and activity trials, 720
statistical methods and assumptions, 723
statistical significance, 725
structured abstracts, 711
study design, 722
study population, 722
titles, 718
treatment assignment, 723
treatment failures, 723
uniformity, 711
utility of the report, 710
writing the paper, 711
representation, 263, 267, 268, 270
guidelines, 272
NIH and FDA guidelines, 272
race and biology, 273
validity and power, 272
reproducibility, 139
research, 13
clinical and statistical reasoning, 17
right to participate, 268
vs practice, 48
Research Ethics Board, 68
research practices, 740
response rates
5-fluorouracil and colon cancer, 254
response surface
dose-finding, 359
retractions, 732, 736
retroactive definitions, 583
retrospective designs, 246
ridge regression, 193
risk, 149, 151
def., 783
difference, 593
estimates of, 592
example, 658
groups, 656, 658
ratio
relative, 593
versus safety, 151
risk–benefit, 103
ratio, 67
rofecoxib, 706, 709
Roman letters, 770
Royal Statistical Society, 84
run-in period, 264
safety, 151, 375
TEMC review, 540
safety and activity trial, 370, 372, 373, 598
Bayesian methods, 447
bias, 184
data-dependent stopping, 455
def., 784
external validity, 195
objectives, 141
randomization, 378
reporting, 720
sample size, 438
skipping, 376
two-stage designs, 456
safety threshold, 152
Salk polio vaccine trial of 1954, 101
sample size, 219, 256, 430, 463, 467, 470, 485
computer programs, 487
CTE trials, 460
def., 783
DF trials, 336
ES trials, 479
event rates, 466
nonadherence, 482
power, 435
for prognostic factor analyses, 660
re-estimation, 425
SA trials, 372
translational trials, 325
versus number of events, 466
sampling, 17
design, 257
SARS, 55
science, 26
versus nonscience, 27
scientific method, 110
misconduct, 738
norms of science, 738
screening trials, 129
seamless design, 426
seeding trials, 27
selection, 421
randomized SA trial, 389
selection bias, 119, 121, 182, 187, 258, 261
comparative trials, 263
treated by randomization, 493
def., 784
literature, 714
quantitative example, 259
selection criteria
quantitative, 262
selection designs, 141
sequential methods
design, 551
fully, def., 776
group, def., 776
sequential probability ratio test, 552
sequential probability ratio test, 556
sham surgery, 117, 122, 123, 239
Shelley, Mary, 25
side effects, 249
ES trials, 401
signal-to-noise ratio, 173
significance test, 174, 202
simulation, 222, 487
skeptical prior, 557
sorafenib, 408, 411
spontaneous improvement, 237
staging, 282, 422
criteria, 248
of development, 278
standardization, 213
standards, 213
error, 139
standing trial
def., 784
statistical analysis system (SAS)
data and programs, 761
statistical bias, 172, 188
correcting, 191
statistical reasoning, 15, 16, 18, 197
statistical significance
def., 784
statistical societies
American Statistical Association, 84
Royal Statistical Society, 84
statistics
def., 784
different perspectives, 198
as science, 16
statistical thinking, 16
stochastic approximation, 339
stopping boundary, 75, 553, 555, 560, 561
stratification, 214, 235, 501
def., 784
excessive, 503
structure
statistical model, 198
use of, 31
study cohort, 254
defining, 255
study duration, 218
subjective probability, 205
subjectivity, 224, 335
subset analysis, 514
sulindac, 607
sunitinib, 411
support intervals, 211
support vector machine, 666
surgical trials, 116, 118, 129
developmental, 116
surrogate outcome, 162, 167, 221, 372, 374, 403
cancer, 164
cardiovascular diseases, 166
def., 162, 784
disease specificity, 164
efficiency, 167
eye diseases, 166
HIV, 166
limitations, 168
uses, 170
survival, 158, 168
curves, 157
nonparametric, 602, 612
time, 156
survivor’s bias, 126
synergy
dose-finding, 357
systematic error, 217
systematic review. see meta-analysis
INDEX
885

tacit knowledge, 14

target population
def., 784

targeted drugs, 12

targeted therapy
def., 784

taylor series
def., 784

TEMCC
charter, 528
temozolomide, 165
terminology, 6, 7, 23, 768
list, 771
thalidomide, 93
theory, 22, 226
therapeutic ignorance
ethics, 72
therapeutic intent, 330
therapeutic ratio
def., 785
therapeutic touch, 110
threshold
def., 785
time dependent covariates, 626, 646
time-to-progression, 159
time-to-recurrence, 159
titration
def., 785
toxicities, 249
DSMC review, 540
translational trials, 302
bias, 321
characteristics, 315
def., 315
empirical entropy, 321
sample size, 325, 436
setting, 314
vs dose-finding, 303
trastuzumab, 165
treatment
def., 785
poorly defined, 243
questionable methods in cancer, 73
unproven, ethics, 72
treatment allocation, 492
discovery, 493
haphazard, 498
practical issues, 493
unequal, 467, 513
treatment combinations, 674
treatment cost, 515

treatment differences, 608
treatment effects monitoring, 78, 522
administration, 527
components, 524
data quality, 540
for efficacy, 541
motives, 523
practical questions, 541
statistical issues, 544
tensions, 525
timeliness, 539
weaknesses, 544
treatment effects monitoring committee, 68,
74, 78, 186, 528, 751
baseline comparability, 538
composition, 531
expertise and objectivity, 535
expertise versus objectivity, 535
masking, 532
meeting format, 533
quality assurance, 540
relationship to investigators, 528
relationship to IRBs, 530
weaknesses, 544
treatment failures
reporting, 722
treatment mechanism (TM) trial
def., 785
randomization, 353
treatment preference
ethics, 77
treatment program, 248
treatment received, 576
analyses, 578
trial design, 217
trialist
def., 2
triangular designs, 560
triple masking, 186
true positive, 379–381, 398
trust, 737
t-test
power and sample size, 459
Tuskegee Study, 58
two-compartment model, 595
two-stage designs, 456
type I error, 141, 175, 176, 178, 194, 433, 459,
560, 562, 565
comparative efficacy trials, 459
control, 154, 176, 630
def., 785
type II error, 175, 177, 178, 194, 433, 459
comparative efficacy trials, 459
def., 785

U.S. Public Heath Service, 58
umbrella trial, 407
def., 785
uncertainty, 218
qualitative versus quantitative, 138
uncertainty principle, 46
univariable
def., 786
univariate
def., 786
univariate analyses
reporting, 723
unproven cancer treatments, 73
urn randomization, 504
utility coefficients, 162

vaccines, 101
valid
def., 786
validity, 397
biological, 246, 752
design, 246, 752
variability, 31, 218
def., 786
variable
def., 786
variances
unequal, 515

vector
def., 786
vitamin C, 73
voluntariness
for informed consent, 68

warts, 109
wash in, 409
washout
def., 786
washout period, 690
wearable technology, 138
Willowbrook State Hospital, 58
window of opportunity, 30
Women’s Health Initiative, 99, 228, 682
World Health Organization, 61
World Medical Association, 58
writing committee, 728

zidovudine, 37