

Index

- Abciximab in Emergency Stroke Treatment Trial-II (AbESTT-II), 246
- abuse liability, 13
- actigraphy, 299, 303
- active arm comparator designs, 265
- active controls, 13, 143, 201–202
- active-control trials, 135
- acute ischemic stroke, 242
- Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN) study, 247
- acute stroke treatment, 243
- recruitment, 252
- acute stroke trials
- consent, 251
- early and middle development studies, 247
- endpoint measures, 245
- recruitment, 252
- subject recruitment, 251
- surrogate consent, 251
- ADAGIO trial, 116–117, 122
- adaptive design, 91, 93, 97, 98, 247
- assessment, 92
- definition, 91
- neurological trials, 96
- sample size re-estimation design, 95
- sample size re-estimation methods, 95
- adaptive design type, 92, 98
- Adaptive Designs Working Group (ADWG), 91
- adaptive dose-finding study, 97
- adaptive randomization, 94, 251
- adaptive seamless design, 95–97
- adaptive trials, 13
- ADAS-Cog, 101
- scale, 230
- score, 32, 230
- adverse drug event
- manufacturer responsibility, 161
- physician reporting survey, 162
- adverse drug event factors, 160–161
- adverse drug event reporting, 163, 164
- statins, 162
- Adverse Event Reporting System (AERS), 163
- aggregate spend, 353
- Albumin in Acute Stroke (ALIAS) trial, 247
- ALS, 273
- biomarker, 278
- disease models, 273
- futility design studies, 279
- lead-in design, 279
- motor neuron death, 273
- mouse model, 273–274
- phenotypic heterogeneity, 275
- selection designs, 279
- symptomatic management, 274
- symptomatic treatment, 282
- therapies, 273
- ALS clinical trials, 273, 275, 279
- dosage, 280
- dropout rate, 281
- drug interactions, 280
- eligibility criteria, 275, 281
- enrollment, 281
- missing data, 278
- random effects model, 278
- sample size, 280
- ALS trial outcome measure, 275
- ALS trials
- statistical techniques, 278
- ALS trials outcome measure
- longitudinal outcomes, 278
- MUNE, 276
- muscle strength, 276
- survival, 276
- vital capacity, 276
- ALSFERS-R, 276, 278
- ALSSQOL, 278
- alternate dosing formulations, 15
- alternative hypothesis, 60
- alternative hypothesis of superiority, 137
- Alzheimer's disease, 11, 14, 19, 25, 29, 113, 132, 203, 204, 227
- behavioral outcomes, 233
- biological signatures, 228
- characteristics, 229
- diagnosis, 229
- diagnostic criteria, 238
- disease-modifying therapies, 238
- molecular changes, 228
- pathology, 227–228
- prevention, 236
- progression, 233
- treatment, 229
- Alzheimer's disease Assessment Scale, 103
- Alzheimer's disease Cooperative Study-Activities of Daily Living (ADCS-ADL), 232
- Alzheimer's disease modification
- randomized withdrawal design, 236
- staggered start design, 236
- trial duration, 238
- Alzheimer's disease trials, 227, 230, 233, 239
- drug safety, 235
- efficacy, 236
- enrollment issues, 237
- minority recruitment, 237
- phase I clinical trials, 234–235
- phase II clinical trials, 235
- phase IIa trials, 235
- phase IIb trials, 235
- phase III trials, 235
- placebo group decline, 237–238
- safety measures, 237
- study partner, 237
- amyloid imaging, 75
- Amyotrophic lateral sclerosis (ALS). *See* ALS
- animal CNS disease models, 21
- animal model, 21–22
- antegrade reperfusion, 243
- antiepilepsy drugs (AEDs), 202
- antiepileptic drug development, 291
- antiepileptic drug safety, 291
- antiepileptic drugs, 284
- mechanism, 285
- antiepileptic drugs trials
- children, 291
- Anti-Kickback Statute, 356
- violation, 357
- Antiplatelet Trialist Collaboration (APTC) endpoint, 170
- any one purpose doctrine, 356
- aplastic anemia, 164
- Appel rating scale, 278
- Arrhythmia Suppression Trial (CAST), 130
- as treated analysis, 66
- aspirin, 6

- asymptomatic intracranial hemorrhage (ICH), 244
- ataluren, 25
- atrial fibrillation, 6
- Avonex Combination Trial, 265
- A β imaging, 25
- A β plaques, 227
- Barthel Index, 245
- baseline severity, 249
- baselines, 108
- basic exposure requirements, 14
- Belmont Report, 174, 183
- BENEFIT Trial, 265
- Best Pharmaceuticals for Children Act (BPCA), 199
- beta-amyloid (A β 1–42), 74
- BEYOND Trial, 265
- bias, 42
- binary outcomes, 107
- biochemical biomarkers, 74
- bio-creep, 143
- bioequivalence, 136
- biological therapies, 5
- biomarker adaptive designs, 95
- biomarkers, 20, 23, 71, 73–74, 127, 243
 - pharmacodynamic markers, 20
 - type 0 biomarker, 23
 - type 1 biomarker, 23
 - type 2 biomarker, 24
- Biomarkers Definitions Working Group
 - conceptual model, 71
- blinding, 43, 45, 136
- blood brain barrier, 22, 23
- blood-CSF barrier, 24
- Bonferroni method, 40
- botulinum toxin, 5
- brain atrophy, 268
- brain imaging, 180
 - incidental findings, 180
 - studies, 11
- brain intervention study risk, 176
- C-11 labeled donepezil, 11
- calcitonin gene-related peptide (CGRP), 97
- calcitonin gene-related peptide (CGRP) receptor, 96
- cancer futility designs, 220
- cancer therapy, 275
- Cardiac Arrhythmia Suppression Trial (CAST), 71, 130
- carotid endarterectomy, 6
- carrier-mediated and receptor-mediated transport, 23
- carryover, 104
- case series, 163
- CDP, 47
- celecoxib, 170
- censored data, 107
- Center for Devices and Radiological Health (CDRH), 206
- central laboratories, 315
- central laboratory criteria, 315
- cerebral beta-amyloid, 11
- cerebral infarction, 242
- cerebrovascular disease, 1
- cGMP regulations, 321
- characteristics of instruments, 76
- child epilepsy, 291
- China, 1
- cladribine, 266
- Class I medical devices, 207, 209
- Class I neurological devices, 208
- Class II medical devices, 208
- Class III medical devices, 209
- clinical trials scope of work (SOW), 312
- clinical care, 174
- clinical data management, 326
- Clinical Dementia Rating Scale (CDR), 232–233
- clinical development, 8, 13, 15, 17
 - early stage, 9
 - late stage, 13–15
 - middle stage, 11, 13
- clinical drug safety trials, 170
- clinical endpoint
 - late phase acute stroke study, 246
- clinical enrollment duration, 342
- clinical equipoise, 175, 176, 178
- Clinical Global Impression, 29
- clinical guidance documents, 16
- Clinical Interview Based Impression of Change (CIBIC), 232
- clinical investigators, 182
- clinical post-marketing safety assessment, 161
- clinical research
 - competent only policy, 192, 193
- clinical research associate (CRA), 311
- clinical research consent, 188
- clinical research organizations (CROs), 312
- Clinical Study Reports (CSR), 347
- clinical supplies, 321
- clinical supply chain, 321
- clinical supply labeling, 323
- clinical trial budget, 316, 317
 - budget management, 319
 - committees, 318
 - components, 317
 - currency fluctuations, 317
 - data management costs, 318
 - IRB/EC costs, 319
 - monitoring budget, 318
 - vendors, 318
- clinical trial design
 - entry and exclusion criteria, 30
 - timeline, 30
- clinical trial team, 309
 - communication, 312
- clinical trials, 1, 2, 5, 9, 29
 - candidates, 177
 - caregiver participation, 182
 - censoring, 36
 - central laboratories, 315
 - cognitively impaired subjects, 192
 - committees, 148
 - critical public engagement, 183
 - data management services, 314
 - data review, 147
 - design, 15, 28
 - design protocol, 28
 - drug safety hypothesis, 169
 - eligibility criteria, 182
 - endpoint, 244
 - enforcement, 352
 - implementation, 338
 - interpretation of results, 201
 - intervention risks, 177
 - investigational agent access, 182
 - management, 312
 - participation, 189
 - patient exclusion, 182
 - payment, 353
 - planning, 319, 327
 - planning process, 309
 - prospective registration, 176
 - publication bias, 348
 - quality assurance system, 344
 - recruitment, 341
 - registries, 348
 - regulatory requirements, 327
 - reporting, 346
 - reporting and transparency, 353
 - results dissemination, 346
 - results publication, 347
 - retention, 342–343
 - safety, 9
 - set-up phase, 320
 - site audits, 344
 - site monitoring, 339–340
 - site qualification, 339
 - site selection process, 39
 - site training, 340
 - subject payment, 343
 - timelines, 319
 - vendors, 316
- clinically isolated syndrome (CIS), 259
- cluster headaches, 101
- CNS drug delivery, 23
- CNS targets, 21
- CNS trial challenges, 173
- CNS trials
 - aggressive interventions, 177
 - ethical research, 183
 - risks, 183
 - trial enrollment, 177

Index

- Code of Federal Regulations, 73
cognitive behavioral therapy for
 insomnia (CBT-I), 296
collateral perfusion, 243
Combination Drug Selection Trial, 85
comorbid insomnia, 295
comparative effectiveness studies, 6
comparative selection trial, 88
complete two-period design, 118
 participant allocation, 120
 statistical model, 118–119
compliance and quality management,
 345
concomitant medications, 10
conditional power, 154–155
confidence interval, 33, 63
confirmatory trials, 93, 98
 adaptations, 94
 confounding, 179
Consolidated Standard of
 Reporting Trials (CONSORT).
 See CONSORT
continual reassessment method, 92
 stopping criteria, 93
continuous outcomes, 106
control group, 30–31, 42
controlled clinical trial, 42
Coronary Drug Project (CDP), 47
correlative and marker studies, 180
covariate adaptive randomization, 94
CRFs, 326
CRM. *See* continual reassessment
 method
 modified approaches, 93
crossover design, 101, 110
 2-treatment 2-period design, 101
 AB:BA design, 103, 107
 matched crossover design, 109
 parallel design, 103
crossover insomnia trials, 301
crossover trials, 101
 applications, 101
 baselines, 109
 logistical challenges, 111
 sample size, 101
 sequence effects, 104
 two-stage approach, 108
 with carryover, 105
 without carryover, 105
CSF measurement, 24
- Data and Safety Monitoring Board
 (DSMB), 94
data monitoring committee, 148, 149
data monitoring committee
 objectivity, 150
data vendor regulation compliance,
 314
database freeze, 320
database lock, 320, 326
- DATATOP study, 114
DATATOP trial, 115, 121
decision-making capacity, 190–191
Declaration of Helsinki, 174–176, 181,
 183
deep brain stimulation (DBS), 218
deep brain stimulation devices, 210
demonstration of effectiveness, 197
Deprenyl and Tocopherol Antioxidative
 Therapy of Parkinsonism
 (DATATOP) trial, 114
device classifications, 322
Disability Assessment for Dementia
 (DAD) scale, 232
disease modification, 113
 modifying effect, 203
 modifying effect study, 203
disease prevention effect study, 204
disease prevention study
 surrogate marker, 204
disease progression treatment, 203
disease-modifying effect, 124
DMC, 159
DMC Charter, 149
donepezil, 101, 107
dopamine agonist, 218
dopaminergic medication, 218, 219,
 222–223
 sleep attacks, 222
dose-response relationship, 11
dose-response study, 96
drop out, 66
drug approval, 197
drug safety, 160
 active surveillance systems, 164, 165
 case definitions, 167
 clinical efficacy trials, 169
 clinical trials, 168
 clinical trials constraints, 168
 drug definition, 167
 observational epidemiological
 study, 165
 post-market clinical trials, 168
 profile trials, 205
 relative risk, 165
 study approach, 171
drug safety issue identification, 161
drug safety profile, 160
drug safety program, 160
drug stability testing, 322
drugs, lack of increase, 3
drugs, cost, 1
DSMB, 96, 98
Duchenne muscular dystrophy
 (DMD), 25
dyskinesias, 218
dystrophin, 25
- early exploratory (phase I) trials, 92
early phase studies
- candidates, 177
 early stage clinical trials, 69
 early trial termination, 154, 345
 Early vs. Late L-dopa in Parkinson
 Disease (ELLDOPA) trial, 115
 ECG vendor criteria, 316
 ECG vendors, 316
 EDSS, 262, 268
 EDSS scale, 262
 effect size, 250
 efficacy, 11, 150, 154
 in vivo model, 9
 proof-of-efficacy-trials, 12
 therapeutic efficacy, 11
 efficacy and safety endpoints, 11
 efficacy trials, 168
 electronic data capture (eDC)
 technology, 345
 eligibility, 48
 eligibility criteria, 249
 endovascular mechanical treatments,
 248
 endpoint, 76, 136
 model, 70
 endpoint selection, 12
 enrichment design, 132
 enrichment design trial
 methods, 127
 enrichment design trials, 127
 advantages, 128, 130, 133
 carryover effects, 132
 complete enriched enrollment, 128
 generalizability, 131
 Kopec mathematical
 model, 129
 limitations, 130
 partial enriched enrollment, 128
 planning considerations, 131
 recruitment efficiency, 131
 responder definition method, 129
 sample size, 129
 sensitivity, 129
 strengths, 129
 subject response, 128
 epilepsy, 284
 photoparoxysmal response, 288
 epilepsy clinical designs
 monotherapy trial design, 292
 epilepsy clinical trials
 adverse event frequency, 287
 assessment of efficacy, 286
 definitive proof of efficacy studies,
 289
 dose-finding study, 289
 drug efficacy, 288
 electroencephalogram (EEG), 287
 exit criteria, 288
 failed trials, 292
 outcome measures, 287–288
 placebo response rate, 292

- populations, 285
 presurgical inpatient study, 289
 quality of life scales, 287
 seizure clusters, 287
 seizure freedom, 288
 sudden unexplained death, 291
 trial duration, 292
 epilepsy drug delivery, 286
 epilepsy drug efficacy studies, 289
 epilepsy drug models, 285
 epilepsy open label extension study, 290
 epilepsy regulatory studies, 289
 epilepsy syndromes, 284
 epilepsy treatment resistance, 284
 Epworth Sleepiness Scale, 222
 equal carryover, 105
 equivalence, 135–137, *See non-inferiority*
 equivalence trials, 135, *See non-inferiority trials*
 eszopiclone (ESZ), 300
 ethical criteria, 187
 ethical study design, 175
 ethics research
 justice, 181
 EU clinical trials, 326
 European Medicines Agency, 16
 evaluable subjects analysis, 65
 Expanded Disability Status Scale (EDSS), 21
 experimental autoimmune encephalomyelitis (EAE), 257
 experimental autoimmune encephalomyelitis (EAE) model limitations, 258
 exploratory outcomes, 29
 fair market value compensation, 352
 false claim billing, 358
 False Claims Act, 357–358
 violations, 358
 family-wise error rate, 150–151
 FCPA, 359
 FDA, 3
 FDA Adverse Event Reporting System, 162
 FDA MedWatch program, 161
 Federal Anti-Kickback Statute.
 See Anti-Kickback Statute
 Federal Drug Agency, 5
 Federal Food, Drug, and Cosmetic Act
 Medical Device Amendments of 1976, 206–207
 Federal Regulations 21 Code, 200
 felbamate, 164
 financial disclosure regulations, 354
 financial disclosure requirement, 354
 fingolimod, 266
 First Subject First Visit (FSFV), 320
 flexible design methods, 152
 focal dystonia, 5
 Food and Drug Administration
 Modernization Act (FDAMA), 197
 Food, Drug, and Cosmetic Act (the Act), 197
 Foreign Corrupt Practices Act.
 See FCPA
 fully sequential designs, 155
 funding mechanisms, 98
 funding research (US), 3
 futility analysis, 81, 154
 futility assessment, 97
 futility design, 78, 80–81, 248
 criterion of superiority, 79
 neuroprotective agents, 78
 sample size, 82
 single-arm design, 79, 84
 two-arm design, 79
 futility design hypotheses, 79
 futility outcome, 81
 sensitivity, 80
 specificity, 80
 type I error, 80
 type II error, 80
 futility design pitfalls, 83
 historical control data, 84
 sample size, 83
 G93A SOD1, 273
 gadolinium-enhancing
 lesions, 257
 Gaucher's disease, 5
 GCP inspections, 343–344
 General Practitioner Research Database, 167
 generalized onset seizures, 286
 genomics studies, 75
 Glasgow Outcome Scale, 59
 global outcome measures, 232
 global statistics, 246
 GMP, 340
 Good Clinical Practice (GCP), 159
 Good Manufacturing Practice (GMP).
 See GMP
 group sequential adaptive
 randomization design, 97
 group sequential methods, 151
 development, 154
 hazard function, 37
 hazard ratio, 38
 Health Canada, 347
 health-related quality-of-life (HR-QOL) scales, 263
 hemorrhagic transformation, 244
 HESDE, 142
 historical controls, 201, 248
 historical evidence of sensitivity
 to drug effects (HESDE).
 See HESDE
 human drug development, 21
 human drug exposures, 22
 human medical research, 174
 policies, codes and regulations, 174
 regulations, 175
 welfare of volunteers, 174
 human pharmacokinetics, 10
 human pharmacology, 10
 human research ethics, 173, 175
 human research risk, 173
 human volunteer studies, 15
 Humanitarian Device Exemption (HDE), 210–211
 Humanitarian Use Device (HUD), 210
 Huntington's disease, 346
 hypotheses, 31
 'one sided' alternative hypothesis, 31
 null hypothesis, 31
 two sided alternative hypothesis, 31
 hypothesis of non-inferiority, 144
 hypothesis tests, 150
 ICH Guideline E3, 141
 IDE application, 211
 IDE exempt studies, 212
 IDE study, 211
 IHASt, 53–54
 imaging biomarkers, 75
 imiglucerase (Cerezyme), 5
 IMP formulation, 323
 IMP quantities, 323
 IMP quantity forecasting, 323
 income of countries, 1
 infarction, 243
 informed consent, 187, 188, 194
 capacity assessment, 190
 decision-making capacity, 190
 emergency exceptions, 253
 probability statements, 189
 subject understanding, 189
 therapeutic motivation, 194
 informed consent forms, 188
 insomnia, 295
 associated conditions, 297
 biomarkers, 299
 diagnosis criteria, 304
 diary data, 302
 intervention goals, 297
 neural pathways, 296
 perpetuating factors, 295
 pharmacologic agents, 297
 precipitating factors, 295
 sleep diaries, 298
 treatment efficacy, 302
 insomnia clinical trials, 297, 299
 blinding, 302
 CBT trials, 300

Index

- comparative effectiveness trials, 305
- comparative efficacy trial, 301
- controls, 304
- dual approach, 301
- duration of treatment, 304
- efficacy, 303
- efficacy and safety, 302
- frequency of assessments, 304
- hypnotic trials, 305
- improvement indicators, 302
- menopausal women, 297
- neurocognitive tests, 302
- psychological interventions, 300
- questionnaires, 298
- recruitment, 303
- retention, 304
- safety outcomes, 305
- sample size, 302
- institutional review board (IRB), 188
- intention to treat (ITT), 46–47
- intent-to-treat (ITT) principle, 136
- strategy, 141
- Interactive Response Technology (IRT). *See* IRT
- interferon β , 259–260
- interim analysis, 49, 151, 157, 250
- sample size, 158
- internal pilot designs, 95
- International Committee on Harmonisation Guidelines, 14
- International Conference on Harmonization (ICH), 163
- intra-class correlation, 103
- Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) 53
- intra-parenchymal delivery, 23
- investigational device exemptions (IDE), 211
- investigational medicinal products (IMP), 317
- Investigational Product (IP). *See* clinical supplies
- investigational research plan, 211
- IP
- accountability, reconciliation and destruction, 325
 - cradle-to-grave tracking, 325
 - storage, 325
 - transportation, 325
- IRB notifications, 346
- IRT, 324
- ischemia, 242
- ischemia trials, 243
- superiority, 250
- ITT strategy, 144
- IV rt-PA pilot study, 247
- Kaplan-Meier curve, 37
- large simple trial, 170
- ibuprofen safety, 170–171
- last observation carried forward (LOCF), 48, 67
- Last Subject Last Visit (LSLV), 320
- late exploratory (phase II) trials, 93
- Latin square design, 110
- L-DOPA, 23
- Lennox-Gastaut Syndrome, 286, 290
- levetiracetam, 285
- Levin-Robbins-Leu (LRL) sequential selection procedures, 86–87
- levodopa, 217–218, 222
- melanomas, 222
- life expectancy, 1
- likelihood-based approach, 111
- linomide, 266
- lipophilic compounds, 23
- log-rank test, 38
- Long-term disability trials, 221
- LRL. *See* Levin-Robbins-Leu (LRL) sequential selection procedures
- Mainland-Gart's approach, 107
- manual muscle testing (MMT), 276
- marginal approach, 107
- masking, 249. *See* blinding
- material corporate events, 346
- maximum tolerated dose (MTD), 92
- Mechanical Embolus Removal in Cerebral Ischemia (MERCİ) trials, 248
- MedDRA dictionary, 326
- medical coding system, 326
- medical devices, 206
- legally marketed device, 209
 - premarket approval, 210
 - regulatory framework, 207
 - substantial equivalence, 209
- Medical Devices Advisory Committee, 213
- Medical Devices Dispute Resolution Panel, 213
- medical devices premarket notification, 209
- metabolomic approaches, 75
- microdialysis, 24
- middle phase studies, 250
- mild cognitive impairment (MCI), 190, 228
- minorities enrollment material, 342
- missing at random (MAR), 66
- missing completely at random (MCAR), 66
- missing data, 66
- missing data mechanism, 111
- missing at random (MAR), 111
 - missing completely at random (MCAR), 111
 - not missing at random (NMAR), 111
- missing not at random (MNAR), 66
- mitoxantrone, 266
- mixed carryover effect., 109
- mixed effects model, 107
- mixed model repeated measures, 123
- MMT, 276
- model-based development, 11
- modified Rankin scale, 245–246
- monotonic spending function, 153
- mortality, 137
- MRI, 76
- MRI measure
- brain atrophy, 263, 264
- MS Functional Composite (MSFC), 262
- MS trials
- adaptive designs, 269
- MTD. *See* maximum tolerated dose
- multi-center trial, 252
- multiple ascending dose studies, 10
- multiple dose studies, 10
- multiple hypothesis testing, 144
- multiple imputation, 67, 123
- multiple sclerosis (MS), 5, 76, 178, 257
- adverse events, 265
 - anti-inflammatory therapy, 258
 - disease free, 268
 - disease-modifying therapy, 258
 - drug development, 258
 - early treatment, 260
 - gray matter pathology, 258
 - hypotheses, 258
 - multiple trials, 266
 - relapse and treatment, 267
 - severity drift, 266
 - subtypes, 259
 - symptom-based therapies, 258
 - MRI measures, 264
 - MRI studies, 263
- multiple sclerosis trials
- enrollment, 260
 - entrance criteria, 260
 - informative enrollment, 260, 262
 - MRI outcome measures, 268
 - recruitment, 266
- multiplicity, 151, 158
- N of 1 trials, 110
- natalizumab, 5, 265
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 174
- National Institutes of Health, 17
- National Multiple Sclerosis Society policies, 178

- NDLM, 96
- NET-PD futility studies, 81, 84
 additive two-arm design, 82
 control group, 81
 placebo parameter, 82
 single-arm study, 81
 two-arm design, 82
- NET-PD network, 78
- neuritic plaques, 227
- neurofibrillary tangles, 227–228
- neuroimaging, 11
- neuroinflammation, 258
- neurointerventional devices, 206
- neurological device market, 206
- Neurological Devices Advisory Panel, 213
- neurological worsening, 244
- neuropathic pain, 19
- neuroprotection, 242, 268
- Neuropsychiatric Inventory (NPI), 233
- Neuropsychological Test Battery (NTB), 231
- neuropsychological testing, 263
- Neuro-QOL projects, 69
- neurostimulation devices, 206
- neurotherapeutics, challenges, 5
- neurotrophic factor development, 20
- New Drug Applications (NDA), 16
- NIH Anticonvulsant Screening Program, 285
- NIH Biomarkers Definitions Working Group, 71
- NIH Toolbox, 69
- NINDS rt-PA acute stroke study, 248
- NINDS rt-PA trial, 246
- no-adverse effect level (NOAEL), 10
- non-inferiority, 142, 250
- non-inferiority margin, 122, 138, 169
- non-inferiority trials, 169–170
 assay sensitivity, 142–143
 choice of margin, 141–142
 patient noncompliance, 141
 sample size, 140
- non-invasive imaging techniques, 24
- non-significant risk device studies, 211
- non-validated CNS interventions, 183
- no-pharmacologic effect dose (NOPED), 10
- normal distribution, 55
- novel therapeutic, 19
- nuisance parameters, 94, 103–105
- null hypothesis, 46, 60
- Numeric Pain Rating Scale, 12
- Nuremberg Code, 174, 176
- observational epidemiological studies, 170
 retrospective cohort study, 166
- observational epidemiological study, 165
 case control studies, 167
 cohort study, 165
 cohort study design, 166
 cohort study restrictions, 166
 confounding, 165
 prospective cohort studies, 166
 retrospective cohort design, 166
- observational epidemiologic study designs
 case-control studies, 165
 cohort studies, 165
- observational epidemiologic study
 case-control study, 168
 nested case-control, 167
- ocular coherence tomography (OCT), 264
- open label dose escalation studies, 247
- Open Report, 148
- open-label dose-escalation studies, 247
- open-label safety extension studies, 15
- ordinal outcome scales
 dichotomous treatment, 246
- ordinal outcomes scales
 trichotomous treatment, 246
- orphan diseases, 200
- orphan drug approval, 200
- orphan drug effectiveness, 200
- orphan drugs, 5
- outcome measures, 69, 76
- outcome-adaptive dose-finding design, 97
- paradoxical insomnia, 298
- parallel group designs, 114
- Parkinson's disease, 1, 19, 101, 107, 113–114, 163, 179, 215
 causes, 215
 comparative effectiveness trials, 222
 confirmatory (phase III) clinical trials, 220
 disability, 219
 early trials, 217
 impulse control disorders, 222
 long term disability trials, 221–222
 medication, 168
 motor complications, 218, 219
 motor features, 215
 neuropathology, 215
 non-motor features, 216
 off time, 218
 phase II clinical trials, 220
 pilot trials, 221
 suicide, 222
- Parkinson's disease modification, 221
 clinical trial, 221
 patient population, 223
- statistical analysis, 221
- Parkinson's disease progression, 219–220, 223
 clinical trials, 220
 monitoring devices, 219
 survival endpoint, 219
- Parkinson's disease trials, 216, 218
 disease progression modification, 219
 missing data, 223
 outcome measures, 219
- partial onset seizures, 286
- passive spontaneous reporting system, 162
- patient follow-up, 137
- patient non-compliance, 141
- patient population, 14
- patient reported outcome (PRO), 12, 69
- patient selection, 11, 249
- Pediatric Research Equity Act (PREA), 199
- pediatric studies, 199–200
- pediatric study safety data, 199
- pediatric written requests (PWRs), 200
- pediatric written responses, 200
- penumbral salvage, 243
- per subject fee (PSF), 318
- per-protocol analysis, 141, 144
- pervasive developmental disorder, 101
- PET imaging studies, 75
- pharmaceutical promotion, 358
- Pharmaceutical Research and Manufacturers of America (PhRMA). *See* PhRMA
- pharmacodynamic marker, 25
- pharmacodynamic modeling, 11
- pharmacodynamic studies, 264
- pharmacokinetic modelling, 11
- pharmacologic agents, 113
- pharmacologic properties, 9
- phase I trial, 177
- phase I trial design objectives, 177
- phase I trial risks, 177
- phase I clinical trials, 74, 264
 approaches, 92
- phase II clinical trials, 74, 264
- phase III clinical trials, 264
- PhRMA adaptive dose ranging studies
 working group, 93
- PhRMA Code, 355
- PhRMA principles, 355
- Physicians Withdrawal Checklist, 12
- Pittsburgh Imaging agent B (PIB), 11
- placebo control trial ethics, 178
- placebo controls, 178
 principles of justice, 181
- placebo group, 202
- placebo response rates, 12

Index

- placebo responses, 179
 placebo-to-match (PTM). *See* PTM
 polysomnography (PSG), 298–299, 303
 population, 53, 54
 population distribution, 54–56
 population parameters, 54
 population standard deviation, 57
 positron emission tomography (PET), 11, 75
 post-market drug safety, 160–161
 pre-approval drug safety assessment, 160
 PRECISION trial, 170
 preclinical experiments, 176
 researcher responsibility, 177
 pre-IDE process, 212
 pre-IDE submission, 213
 premarket approval (PMA), 214
 primary insomnia, 295
 primary outcome, 29
 primary progressive multiple sclerosis (PPMS), 257, 260
 principal investigator (PI), 311
 principle of responsiveness, 181
 PROACT I, 243
 progressive multifocal leukoencephalopathy (PML), 265
 project manager (PM), 309
 proteomics, 75
 protocol feasibility, 338
 PROUD trial, 116, 118
 pseudo-placebo withdrawal study, 290
 PTM, 322
 public Advisory Committee meetings, 16
 Public Health Service Act, 197
 putative disease related pathways, 21
p-value, 65

 QALS trial, 85
 quality control monitoring, 46
 Quality of Life-AD (QOL-AD), 234

 radio-labeled receptor ligands, 24
 random effects models, 107
 random error, 42, 44, 45, 50
 randomization, 65, 136
 randomization allocation ratio, 249
 randomized clinical trial, 31, 135
 randomized controlled stroke trials, 247
 randomized controlled therapeutic trials, 147
 randomized controlled trial, 136, 178
 randomized start trials, 128, 204
 randomized withdrawal trials, 204
 outcome measure, 202
 rapid endpoint, 85
 recanalization, 242, 243

 recruitment and retention plan, 341
 recruitment and retention plans, 342
 regression models, 67
 regulatory reporting requirements, 347
 relative risk. *See* hazard ratio
 remyelination strategies, 258
 Request for Proposal (RFP), 312
 research ethics, 174
 fair research design, 181
 justice, 181
 principles, 175
 research participants, 3
 Resource Utilization in Dementia (RUD) scale, 233
 response adaptive design, 109
 response-adaptive randomization, 94
 reverse multiplicity problem, 144
 reverse placebo effect, 131
 rhabdomyolysis, 166
 riluzole, 280
 routine trial closure, 341, 345
 RRMS trials
 placebo-controlled trials, 265
 relapse number, 262
 rt-PA treatment, 251

 safe harbor rules, 357
 safety and tolerability issues, 12, 15
 safety and tolerability profile, 14
 safety endpoints, 69
 safety of research participants, 356
 safety or tolerability issues, 11
 safety pharmacology studies, 9
 safety studies, 155
 sample mean, 52
 sample size, 33, 94, 250
 sample size adjustment, 251
 sample size re-estimation, 15
 statistical analysis plan, 327
 schizophrenia, 19
 secondary outcomes, 29
 secondary progressive MS (SPMS), 257
 Securities Exchange Act of 1934, 346
 seizure diary, 286–287
 seizure prophylaxis, 6
 seizures, 284
 selection design, 78
 selection of endpoints, 76
 selection procedures, 84–86
 indifference zone approach, 85
 sequential selection procedures, 85
 sensitivity analyses, 48
 sequential monitoring, 94
 serious adverse events (SAEs), 161, 244
 serotonergic effects, 11
 serotonin-norepinephrine reuptake inhibitors, 11

 severe impairment battery (SIB), 232
 sham control studies, 223
 sham surgical approach, 43, 218
 sham surgical controls, 179, 223
 conditions of use, 179, 180
 ethical critique, 179
 intervention studies, 179
 shift analysis, 246, 247
 sICH, 250
 significance level, 62, 151
 significant risk device, 211
 simple carryover, 110
 simple random sample, 54
 single ascending dose studies, 9
 single dose studies, 10
 single imputation, 67
 single photon emission computerized tomography (SPECT), 75
 single treatment arm studies, 248
 site coordinator, 312
 site manager (SM), 311
 Site Monitoring Visit (SMV), 340
 sliding dichotomy analysis, 246
 SMV, 341
 societal benefit, 3
 solanezumab, 25
 spending functions, 153
 SPORTIF III trial, 138, 141–142
 standard deviation, 53
 standard of care (SOC) costs, 318
 state biomarker, 73
 statistical software, 155, 157
 EAST, 157
 ldBounds package, 155
 R-project, 155
 SAS, 156
 statistics, 52–53
 step-forward randomization, 252, 252
 stopping boundaries, 152, 155, 157
 Haybittle-Peto method, 152
 O'Brien and Fleming method, 152–154
 Pocock method, 152, 154
 stratification factors, 48
 stroke prevention, 6
 stroke prevention trials, 253
 Stroke Prevention using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III trial. *See* Sportif III trial
 Stroke Therapy Academic Industry Roundtable (STAIR) recommendations, 242
 Stroke–Acute Ischemic NXY Treatment II (SAINT II) trial, 246
 stroke-specific outcome measures, 245
 structural imaging, 76
 Student's *t*-distribution, 55

Cambridge University Press

978-0-521-76259-5 - Clinical Trials in Neurology: Design, Conduct, Analysis

Edited by Bernard Ravina, Jeffrey Cummings, Michael P. McDermott and R. Michael Poole

Index

[More information](#)

Index

- study forms, 46
 substantial evidence of effectiveness, 197
 clinical trials, 200–201
 single trial elements, 198
 single trials, 198
 sufficient washout periods, 107
 Sunshine Act, 353
 superiority, 250
 superiority to placebo, 142
 superiority trial, 137
 patient noncompliance, 140
 sample size, 140
 surrogate consent, 191
 surrogate endpoint, 71
 surrogate markers, 198, 203
 clinical outcomes, 198, 199
 studies, 198
 surrogate outcome measures, 71
 symptomatic and disease-modifying effects, 113
 symptomatic intracranial hemorrhage (sICH), 244

 T2 hyperintense lesions, 263
 Tacrine Consortium study, 132
 tau, 227
 TEMPO trial, 116
 test of significance, 32
 therapeutic development, 19
 therapeutic development programs, 71
 therapeutic misconception (TM), 193

 time to event trial, 290
 tissue plasminogen activator, 97
 TNK trial, 251
 TOAST (III) trial, 147, 150
 data monitoring committee, 149
 tolerability profile, 10
 tolerable dose range, 10
 trait biomarker, 73
 treatment approval, 203
 treatment by period interaction, 104
 trial monitoring, 159
 trial termination, 159
 Tufts quantitative neuromuscular examination (TQNE), 276
 two-arm non-inferiority trial
 sample size, 140
 two-period design, 114, 221
 ADAGIO trial, 120
 additional treatment, 121
 delayed start design, 116, 118
 eligibility criteria, 120
 evaluation, 121
 limitations, 124–125
 missing data, 123
 multiple statistical testing, 122
 period duration, 120
 primary analyses, 121–123
 PROUD, 120
 sample size, 124
 withdrawal design, 115, 116
 two-stage adaptive dose-ranging design, 96

 type I error, 61, 150, 151
 type II error, 61

 UK Bribery Act, 359
 unblinding, 132
 unequal carryover, 106
 unexpected adverse drug events, 161
 Unified Parkinson's Disease Rating Scale (UPDRS), 216, 219
 United States drug safety system, 161
 unvalidated surrogate markers, 198
 US Physician Payments Sunshine Act (Sunshine Act), 353

 variability, 53
 variance, 53
 virtual biotechnology firms, 5

 warfarin, 6
 washout periods, 132
 Wilcoxon-rank sum test, 106
 women and minority participation, 342

 ximelagatran, 138, 141

 zolpidem, 301

 α spending function, 153, 154