

Index

Note to index: An f following a page number designates a figure; a t following a page number indicates a table.

```
\alpha[alpha], 380. See also hypothesis testing
                                                    authorization form for protecting data, 18,
\beta[beta], 381–82. See also hypothesis
                                                               36-37
          testing
                                                    avoiding bias. See bias, avoiding
adherence, 168-71, 284-94
  adherence assessment, 286-89
                                                    Belmont Report, 16-17
     to clinical schedule, 289
                                                    bias, 203-16
     with direct observation, 286-88
                                                       analysis bias, 212-13
     without direct observation, 288-89
                                                       assessor bias, 211-12
  efficacy vs. effectiveness, 284-86
                                                       avoiding
  ethical issues, 293-94
                                                         assessment methods and training, 223-24
  key points, 294
                                                         blinding (masking), 143-44, 221-22
  measures to improve, 289, 293
                                                         data monitoring during study, 224-25
  per protocol analysis, 285-86
                                                         ethical issues, 225-26
  See also recruitment and retention
                                                         key points, 226
allocation bias. See prognostic bias
                                                         population selection, 217-19
alternative hypothesis, 378. See also hypothesis
                                                         randomization, 143-44, 219-21
          testing
                                                       care provider bias, 210-11
analysis bias, 212-13
                                                       in case-control study, 204-05, 218, 222, 307-
archiving requirements, 372
                                                              08, 315
assent, 39. See also informed consent
                                                       in cohort study, 222
assessor
                                                       common sources, 203-13
  bias, 211-12, 222
                                                       and data storage, 371
  training of, 223-24
                                                       ethical issues, 214-15
```

403



More Information

bias (cont.)	maintaining the blind, 335–37
historical controls, 206, 219, 317-18	what to blind, 334
and hypothesis testing, 387	when not possible, what to do, 337-38
interpretation bias, 213	reasons to use, 143-44, 221-22, 258-59
in interventional study, 143-44	blinding techniques for interventional study,
in interviews, 219, 223	270-83
key points, 215–16	common problems maintaining blinding, 279-81
laboratory bias, 212	efficacy, 280
learning effect, 209-10, 224	leaks and guesses, 281
non-differential bias, 214	side effects, 279-80
overlap among types of, 203	of data management staff, 275
participant bias, 208	ethical issues, 281-82
prognostic bias, 204-06	of intervention, 270–75
publication bias, 203, 213, 215	non-pharmaceutical intervention, 273-74
random variation vs., 203	pharmaceutical intervention, 270-73
and randomization (see randomization)	key points, 282-83
recall bias, 208-09, 218-19, 301-02	of laboratory staff, 274-75
rater bias, 211–12	of treatment, 270–75
selection bias, 206-08	non-pharmaceutical treatment, 273-74
underreporting as, 209, 308	pharmaceutical treatment, 270-73
See also ethics; randomization; validity	treatment provision, 275–78
binary variables, 175, 190-91	by institutional pharmacist, 276-77
blinding, 258-69	by manufacturer, 276
breaking the blind, 266-68	by study team, 277-78
ethical issues, 268	blocking, 252-54
hierarchy of, 259-66	benefits and pitfalls with, 254-55
complete blinding, 261-62	and interim analyses, 253
double-blind study, 260-61, 334	reason for, 250
open-label study, 264–66	breaking the blind, 266-68
in interventional study (see blinding	
techniques for interventional study)	care provider bias, 210–11
single-blind study, 262-64	carryover effect, 75. See also crossover study
key points, 269	case-cohort study, 127-28
level of blinding, multiple, 266	case-control study, 51-52 95-103
in observational study, 334–39	advantages of, 86, 100-01
ethical issues, 338	basic design of, 95-97
key points, 339	bias in, 204-05, 208-09, 218, 222, 307-08, 315



More Information

Cambridge University Press 978-0-521-84063-7 — Planning Clinical Research Robert A. Parker , Nancy G. Berman Index

405

Index

key points, 319-20 cohort study vs., 100-01, 127-29 control groups, multiple, 96-97, 316 nested, 317 concurrent vs. historical controls, 95 sample size, 318-19 data issues in, 114-15, 128-29 special situations, 316-18 disadvantages of, 100-01 case series study. See single arm study ethical issues, 102 censored data, 193 key points, 102-03 children matching in, 98-99, 321-33 age as inclusion and exclusion frequency matching, 99, 328-29 criterion, 152 individual matching, 98-99, 321-33 and assent, 39 nested, 99-101, 127 exclusion from study, 158-59 participant recruitment, 128 and informed consent, 35, 38-39, 149, 158 record reviews as, 112, 130, 132 clinical equipoise, 121 research question as determinant of, 54, 119-20 clinical importance vs. statistical significance, resource issues, 124 380 clinical trials, 52-53 time considerations, 129 uses of, 95 phases of, 53 variables in, 182 code book, 362 verification of data, 371 coding, data, 184, 191-92 See also case-control study, participant coercion, 37. See also informed consent identification; matching cohort study, 50-51, 82-94 case-control study, participant identification, advantages compared to interventional study, 97-98, 307-20 86-87 case identification, 97, 308-10 basic designs, 82-86 control identification, 311-13 and blinding, 222 general considerations, 97-98 case-control study vs., 100-01, 127-29 multiple control groups, 96-97, 316 concurrent, 82-83 (see also prospective ethical issues, 319 cohort study) general considerations, 307-08 cross-sectional study vs., 108 bias, 307-08, 315 data problems in, 114 historical controls, 317-18 disadvantages compared to interventional inclusion and exclusion criteria for controls, study, 87-89 313-16 ethical issues, 92-93 and bias, 315 historical, 82-83 (see also retrospective cohort and definition of "normal or healthy," study) 155-56, 314-15 key points, 93-94 and definition of "standard," 315 outcome variables, 192



cohort study (cont.)	concomitant variables. See predictor and
participant recruitment, 128, 299-300,	confounding variables
304-05	confidentiality, 22
prognostic bias in, 205-06	in case-control study, 308-10
prospective 82-83 (see also prospective	communication with participants
cohort study)	general, 171
retrospective cohort study, 82-83 (see also	and Internet communication with
retrospective cohort study)	participants, 172
variables in, 181, 182, 192, 197	in cohort study, 305
verification of data, 371	and data storage, 371-73 (see also data
See also cohort study, participant	storage: confidentiality)
identification; record review	informed consent, 31, 34
cohort study, participant identification,	examples of, 34
297–306	record review, 118
comparative cohort study, 304-05	during recruitment and retention, 171-72,
data	173
availability, 297–300	Study ID, 246, 343-44, 372
completeness, 302	See also informed consent
quality, 300	conflict of interest, 36
in prospective study, 297–98, 299	confounding variables. See predictor and
in retrospective study, 298, 299	confounding variables
sources, 299	consent. See informed consent
ethical issues, 305-06	control group
key points, 306	in case-control study, 97-98 (see also
multiple cohort study, 304-05	case-control study, participant
stratified sampling, 299-300	identification)
study time line, 302–04	in comparative cohort study, 304-05
Common Rule (The Federal Policy for the	in interventional study
Protection of Human Subjects),	(see randomization)
17, 23, 118	intervention, 229–36 (see also intervention
comparative cohort study, 86	control)
compensation for participants, 16, 30–31, 169	convenience allocation as not randomization,
compliance. See adherence	242
computers	Council for International Organizations of
and confidentiality, 372, 373	Medical Sciences (CIOMS), 15
and data storage, 358-74	crossover study, 48-49, 53, 74-77
programs for, 249	AB/BA design, 74-75



etnical issues, 80	computer records, 3/2
participant recruitment, 76-77	and data sharing, 372-73
problems with, 75-76	images, 372
study question for, 63, 64	participant right to withdraw use
cross-sectional study, 52, 104-10	of data, 372
cohort study vs., 108	and Study ID, 372
common problems in, 108-09	documenting data, 362
ethical issues, 109-10	ethical issues, 373
key points, 110	key points, 374
See also record review	numeric vs. alphabetic codes, 369
	program selection, 364-65
databases. 358-61	terminology for, 358
data collection, 343-57	verifying data, 367-71
ethical issues, 355–56	and bias, 371
key points, 356–57	abstraction of source documents, 367-68
Manual of Procedures (MOP), 176, 183, 351, 354	comparison of computer data to original
methods, 344-52	records, 368
biological tests, 351	consistency and plausibility, 367, 368-70
interviews (see interviews)	uncorrectable variables, 370-71
other types of procedures, 351–52	Declaration of Helsinki, 15-16
questionnaires (see questionnaires)	Department of Health and Human Services
smartphones 345-46	(HHS), 17, 18, 26, 38
tablets 345–46	dependent variables. See outcome variables
noise in, 214, 392	derived outcomes, 184, 190-92. See also
Study ID, 246, 343-44, 372	outcome variables
See also data storage; variables	design development
data dredging, 194, 212-13, 387	interventional study, 69-71
Data Safety and Monitoring Board (DSMB), 14,	multiple designs considered, 130-32
25–26, 213, 267, 280	record review, 130-32
data storage, 184-85, 358-74	design selection, 119-33
basic approaches to, 358-61	ethical issues, 132–33
analysis programs, 361	interventional compared to observational
relational databases, 359, 360-61	design, 54-57, 86-89
spreadsheets, 359, 360, 361	interventional study, 120-24
capturing data for storage, 365-67	development, example, 69-71
confidentiality, 371–73	ethical issues, 120
archiving requirements, 372	practicality of, 123



design selection (cont.)	effectiveness, 284–86
adequate number of participants, 124	efficacy, 284-86
resource issues, 123-24	elderly persons
time issues, 123	recruitment of, 168
selection of, 124–27	electronic devices for data collection, 345-46
parallel group study, 125	endpoints. See outcome variables
pre-post study, 125-26	equivalence study, 63, 392
randomized vs. non-randomized, 125-26	errors, statistical. See hypothesis testing
single arm study, 125	ethics, 14–27
key points, 133	additional reading, 26
multiple designs, 119-20, 130-32	addressing before start of research, 12-13
observational compared to interventional	adherence, 293-94
design, 54-57, 86-89	case-control study, 102
observational study, 127-30	participant identification, 319
adequate number of participants, 124	cohort study, 92-93
case-control vs. cohort study, 100-01,	defining populations for, 305-06
127–29	compliance, 293-94
ethical issues, 120	crossover study, 80
prospective vs. retrospective cohort study,	cross-sectional study, 109-10
90-92, 127-30	data collection, 355-56
resource issues, 123-24	Data Safety and Monitoring Board, 14, 25-26,
time issues, 123	213, 267, 280
devices for data collection, 345-46	data storage, 373
dichotomous variables, 175, 190–91	design selection, 120, 132-33
documentation. See authorization form for	development of guidelines for, 14-18
protecting data; informed consent	international codes, 15-16
document; institutional review board,	Council for International Organizations
approval	of Medical Sciences, 15
double-blind study, 260-61. See also blinding	Declaration of Helsinki, 15–16
dropouts	Nuremberg code, 15
large impact in crossover study, 76	United States, 16–18
and number to be randomized, 247	Belmont Report, 16–17
DSMB, 14, 25–26, 213, 267, 280	Health Insurance Portability and
	Accountability Act, 17–18
economic issues	National Research Act, 16-17
and blinding, 281	Standards for Privacy of Individually
and generalizability, 141, 142	Identifiable Health Information, 17-18



More Information

409 Index

duration of study, 194-95 fetuses and neonates, 31, 40-41 generalizability, 144-45 Food and Drug Administration (FDA), 18, 24, informed consent, 42-43 (see also informed 26, 215, 233 consent) frequency matching, 328-29 interventional study, 80, 120 IRB (see Institutional Review Board (IRB)) generalizability, 137-43 key points, 26-27 definition, 137 observational study, 92-93 economic issues in, 141, 142 blinding, 332-33 ethical issues, 144-45 outcome variables, 194-95 key points, 145-46 placebos, 281-82 and population studied, 137-40 principles, 18-22 study procedures, 140-43 fair subject selection, 20 assessment methods, 142-43 favorable risk-benefit ratio, 21 treatment and treatment monitoring, 140-42 independent review, 21 See also validity informed consent, 22 (see also informed consent) Health and Human Services (HHS), 17, 18, 26, 38 respect for potential and enrolled subjects, Health Insurance Portability and Accountability Act (HIPAA) scientific validity, 19-20 and data protection, 36-37, 298 social and clinical value, 18-19 and informed consent, 31-32, 35, 305 record reviews, 118 purpose of, 17-18 recruiting and retaining participants, "healthy" control, definition of, 155-56, 314-15 HHS, 17, 18, 26, 38 resources for additional information, 26 HIPAA. See Health Insurance Portability and safety variables, 185 Accountability Act (HIPAA) sample size, adequacy of, 400 historical controls, 95, 206, 219, 317-18 study design selection, 59-61 hypothesis driven research, 7, 11-12 study population, 158-59 hypothesis testing, 377-89 tissue samples, 41-42 alternative hypothesis, 378, 379-80 validity, 145 one-sided vs. two-sided, 379-80, 383, 388 variables, use of, 185 criminal trial as analogy for, 377-78 examples. See book website for searchable index ethical issues, 387-88 potential for bias, 387 FDA, 18, 24, 215, 233 testing until you find significance, 387-88 The Federal Policy for the Protection of Human key points, 388-89 Subjects (Common Rule), 17, 23, 118 null hypothesis, 378, 379



hypothesis testing (cont.)	waiver of informed consent, 42, 118, 123
overview of, 378-82	and undue influence, 37-38
P-value, 382, 383–84	See also informed consent document;
process for, 383-86	Institutional Review Board (IRB)
power, 382	informed consent document
reject vs. fail to reject null hypothesis, 378-79	authorization form for protecting data, 18,
statistical significance	36–37
vs. clinical importance, 380	elements of, 30-32
determining, 383-86	examples of text for
Type I error, 380–81	confidentiality, 34
Type II error, 381–82	investigator and participant interactions at
	end of study, 33
inclusion and exclusion criteria. See study	procedures in study, 32-33
population	restrictions on immediate withdrawal from
independent review, 21	study, 33-34
independent variables. See predictor and	language used in 29
confounding variables	level of detail expected, 32-33
informed consent, 22, 28-43	and reading level of participant, 29-30
and coercion, 37	release to use data, included in 18, 36-37
and cohort study, 305	templates for, 30, 32
and confidentiality, 31	institutional questionnaires, 346
ethical issues, 22, 42-43	Institutional Review Board (IRB), 14, 16, 18
exemption or postponement of, 42, 149	approval required for
and IRBs, 24, 42	cross-sectional study, 109
key points, 43	cohort study, 298, 305
process, 28-36	interventional study, 58, 123
consent document, 29-34	record review, 111, 115, 118
interview, 34–36	composition of, 23-24
special populations, 38-41	establishment of, 23
children, 35, 38-39, 149, 158	exemption or postponement of informed
persons unable to understand and agree to	consent, 42, 149
study, 39, 149, 158	and financial compensation for participants,
pregnant women, fetuses, neonates, 31,	169, 173
40-41	overview of, 23-24
prisoners, 41	private for-profit, 23
speakers of other languages, 35, 40	purpose of, 24
for tissue sample use and retention, 41–42	responsibilities of, 24



More Information

and risk-benefit ratio, 58, 60-61	blinding techniques for, 270-75 (see also
and safety monitoring plan, 180	blinding techniques for interventional
and special populations, 38, 40	study)
and undue influence, 37-38	case series study, 64-66 (see also single
and waiver of informed consent, 42,	arm study)
118, 123	confounding variables in, 178
See also Data Safety and Monitoring Board	crossover study 74-77 (see also crossover study)
(DSMB); ethics	ethical issues, 59-61, 80, 120
instrument, definition of, 345	focus of, 47
Internet communication with	key points, 61, 81
participants, 172	outcome variables in 177 (see also outcome
interpretation bias, 213	variables)
intervention, control, 229-36	overview of, 47-49, 62-63
describing, 234-35	parallel group study 69 69-70 (see also
active controlled study, 234	parallel group study)
placebo controlled study, 234	participants, all receive intervention, 64-68
ethical issues, 235	with randomization
placebo control group, 235	crossover study 74-77 (see also crossover
key points, 235-36	study)
problems in, 229-31	without randomization
standard of care, 230-31	pre-post study 77–79
taking of medication, 229-30	single arm study, 47-48, 64-66 (see also
selecting, 231–33	single arm study)
active control group, 231, 233	participants, some receive intervention 68-74
placebo control group, 231, 232-33	parallel group study 69-70 (see also parallel
See also interventional study	group study)
interventional study, 62-81	participants with and without intervention,
advantages of, 57	74–79
bias in, 143-44	with randomization
avoiding (see blinding techniques for	crossover study, 74-77 (see also
interventional study)	crossover study)
types of	without randomization
historical controls, 219	pre-post study, 77-79
learning effect, 209–10	predictor variables in, 196
prognostic, 204	pre-post study, 77-79
recall, 208	randomization in, 48
blinding in (see blinding)	with randomized intervention



More Information

interventional study (cont.)	learning effect, bias due to, 209-10, 224
crossover study, 74-77 (see also crossover	list matching, 325
study)	
parallel group study, 69-70 (see also	Manual of Procedures (MOP), 176, 183, 351, 354
parallel group study)	masking. See blinding
without randomized intervention	matching, 321–33
pre-post study, 77–79	definition, 321
single arm study, 47-48, 64-66 (see also	ethical issues, 332–33
single arm study)	frequency matching, 328–29
and risk-benefit ratio, 122	index group, 322-23
safety variables in, 179	individual matching, 325-28
single arm study, 64-66 (see also single	choosing between eligible controls, 327–28
arm study)	using distinct characteristics, 327
summary of, 47-49, 62-63	using scores, 327-28
time line for, 302-03	defining matching criteria, 325-27
variables in, 176–81	using difference score, 326
confounding, 178	using distinct characteristics, 325-26
outcome, 177	using propensity score, 326-27
predictor, 177-78, 196	using variable scores, 326
predictor vs. confounding variable, 181	key points, 333
role of variables, 180-81	list matching, 325
safety, 178	practical issues, 329-32
and verification of data, 371	appropriate controls, lack of, 331-32
See also randomization; blinding	data analysis, 332
interviews	excessive matching criteria, 330
and blinding, 336-37	overmatching, 329-30
free-form, 348-51	recruitment of controls from general
interviewer training, 350–51	population, 331
language issues, 351	selection of controls from databases, 330-31
transcribing and coding, 349-50	reasons to use, 321–22
structured, 349	when done, 323–25
and bias, reducing, 219, 223	in analysis phase, 324–25
and cross-training of raters, 223-24	in recruitment phase, 323-24
as data collection instrument, 345	minimizing bias. See bias, avoiding
scoring of, 349	
	National Commission for the Protection of
laboratory bias, 212	Human Subjects of Biomedical and
language issues. See speakers of foreign languages	Behavioral Research, 16-17



More Information

413 Index

National Institutes of Health (NIH), 23, 26 retrospective vs. prospective cohort study, neonates and fetuses, 31, 40-41, 152 90-92, 127-30 nested case-control study, 63, 99-101, 127 selection of exposures, 49-50 NIH (National Institutes of Health), 23, 26 variables, 181-82 noise in data, 214, 392. See also sample size See also case-control study; cohort study; non-differential bias, 214 cross-sectional study; prospective non-inferiority boundary, 233 cohort study; retrospective cohort non-inferiority study, 63, 71-72, 392 study "normal" control, definition of, 155-56, 314-15 Office for Human Research Protection null hypothesis, 378. See also hypothesis testing (OHRP), 26 Nuremberg code, 15 open label extension, 73 open label study, 264-66. See also blinding observational study outcome variables, 177, 187-95 bias in and data recoding, 184, 191-92 assessor, 211-12 and data relevance, 188 historical controls, 219 defining, 187-90 prognostic, 204-06 derived, 188-89, 190-92 recall, 208-09 changes over time, 192 blinding in, 334-39 dichotomous outcomes, 190-91 ethical issues, 338 efficacy, distinguishing from safety key points, 339 variables, 187 maintaining the blind, 335-37 ethical issues, 194-95 what to blind, 334 and frequency of measurements, 190 when not possible, what to do, 337-38 in interventional study, 188, 198 case-control study, 96 (see also case-control key points, 195 study) multiple equally important, 189 case-control vs. cohort study 100-01, 127-29 in observational study, 182, 189 as predictor variables, 180-81, 197-98 cohort study, 82-83 (see also cohort study; prospective cohort study; primary vs. secondary, 177 retrospective cohort study) safety variables as, 178, 180 cross-sectional study, 105 (see also crossspecifying in advance of study, 187-88, sectional study) 194 designs for, 49-52 surrogate, 193-95 ethical issues, 92-93, 102, 118 time-related outcomes, 192-94 and informed consent, 30 time-to-event, 193 key points, 93-94, 102-03, 110, 118 time trends, 192-93 record review, 115, 116 (see also record unexpected results, 194 review) overmatching, 329-30



More Information

414 Index

paper-based questionnaires, 345 ethical issues, 200-01 parallel group study, 69-70 and excessive data collection, 201 need to collect, 185 basic design, 48-49, 68-74 and blinding, 68-69 in interventional study, 181 and clinical trials, 53 key points, 201-02 drop out problem in, 70 in observational study, 322 ethical issues, 80 predictor variables, 177-78, 196-98 with extension, 73 72-73 in interventional study, 196, 197, 198 outcome variables as, 180-81, 197-98 intervention vs. control group in, 68 and randomization, 68, 73-74 in observational study, 196 selection of, 124-27 primary and secondary, 177-78 variables, uses of, 175-76, 188, specifying in advance of study, 196, 200-01 197, 198 pregnancy See also interventional study and informed consent, 31, 40-41 and pharmaceutical interventions, 155 pharmaceutical interventions and blinding, 261, 270-72, 276-77 pre-post study, 77-79 and pregnancy, 155 prisoners, and informed consent, 41 Phase 1 clinical trial, 53, 264-66 privacy 17-18, 24, 298, 372. Phase 2 clinical trial, 53 See also confidentiality Phase 3 clinical trial, 53 authorization form for protecting data, 18, Phase 4 clinical trial, 53 PHI (Protected Health Information), 17-18 prognostic bias, 204-06, 219-21 pilot study, 264-66 prognostic variables, 240, 249-50 placebo control study, 231, 232-33, 234, 235 proof of concept study, 65 propensity score, 326-27 placebos as control group 231, 232-33, 234, 235 prospective cohort study, 82-83 ethical issues with, 281-82 comparative cohort study, 86 population. See special populations; study data quality issues, 129 population long-term outcome, example, 83-84 post-marketing study, 53 recruitment for, 297-98, 299 power, 382. See also hypothesis testing resource issues in, 124 post-hoc matching, 324-25 vs. retrospective, 90-92, 127-30 predictor and confounding variables, 178, 196-202 routinely collected data for, 85 confounding variables, 198-99 short-term outcome, example, 84-85 examples of, 199 study time line for, 303 in observational study, 182, 199 time issues in, 129 distinction between, 181, 199-200 See also cohort study



More Information

Protected Health Information (PHI), 17–18	key points, 25/
Authorization Form for use of, 18, 36-37	randomization schedule
publication bias, 203, 213, 215	adding special features to, 249-55
	blocking, 252-54
question, research. See research question	benefits and pitfalls with, 254-55
questionnaires, 345–48	and interim analyses, 253
common problems, 108	reason for, 250
as data collection instrument, 345	creation of, 246–49
designing, 347-48	randomization number, 246-47
electronic devices, 345-46	Study ID number, 246
formatting, 346	treatment assignment list, 248
institutional, 346	number of randomization numbers in, 247
language issues, 347-48	randomization numbers of dropouts are
minimizing recall bias, 219	not reused, 248-49
for subjective data, 346	stratification, 250-52
	benefits and pitfalls with, 254-55
random variation, bias vs., 203	defining strata, 250-51
randomization, 237-44	separate randomization schedule for
assessor bias, 243	each stratum, 251–52
and blinding, 238, 278	reason for, 250
convenience allocation is not, 242	randomized interventional study. See
defining, 237-40	interventional study
to eliminate bias, 143-44, 219-21, 240-42	randomized parallel group study. See parallel
prognostic bias, 238, 240, 241-42	group study
prognostic variable balance, 240, 249-50	rater bias, 211-12, 222
selection bias, 240-41	recall bias, 208-09, 218-19, 301-02
key points, 244	recoding variables, 184, 191-92
participant bias, 243	record review, 111–18
reasons for, 242-43	data
requirements for valid, 245-46	availability, 111–13
treatment unknown until participant	problems, 114–15
enrolled in study, 246	quality, 113
techniques for (see randomization	design development, example, 130-32
techniques)	case-control study, 130, 132
unequal, 253, 255-56, 399	morphing into prospective cohort study,
randomization techniques 245-57	92, 131
ethical issues, 256–57	retrospective cohort study, 130-31



More Information

record review (cont.)	relational databases, 359, 360-61
ethical issues, 118	research
IRB approval for, 111, 115	broad issues in, 3-4
key points, 118	assessment of success, 4, 11-12
observational study, 52	capability to achieve goal, 4, 10-11
observational study, examples of, 115-18	justification of research, 4, 9
case-control study, 116, 117	reasons for doing, 3-4, 5-7
cross-sectional study, 115-17	ethical issues in, 12–13
retrospective cohort study, 115-17	issues to address before starting, 3-13
recruitment and retention, 161-74	key points, 13
as part of planning, 163–64	See also research question
longitudinal study, 163	research question, 4, 7–8
ethical issues, 172–73	abstract as way to clarify, 7–8
and generalizability, 137–40	framing may limit designs, 54-57
key points, 174	multiple designs possible for one, 119-20
methods, 164-68	multiple research questions from a single
advantages and disadvantages of, 165-66	study, 53-54
from clinics, 164-66	impact on design selected, 53-57, 63-64,
from cohort study, 128	119–20
from databases, 330-31	resource issues, 123-24. See also economic
from general population, 166-67	issues; time considerations
Internet, use of 171–72	retention. See recruitment and retention
random digit dialing, 167-68	retrospective cohort study, 82-83 90-92
right number for, 161-63	advantages of, 86-87
flow of participants, example, 162	data collection, 104
websites, 167	data quality issues, 129
retention, 168-71	vs. prospective cohort study, 90-92, 127-29
and alternative contact methods, 171	resource issues, 124
and financial compensation, 169, 173	speed of results, 129
and long periods between study visits, 169-71	study time line, 302-04
methods to improve, 293	See also cohort study
study flexibility, 171	risk-benefit ratio, 21, 60-61
right to leave the study, 173	and blinding, 268
special populations, 168	and Institutional Review Board (IRB), 58,
staff role, 163-64	60-61
See also adherence	and interventional study, 122
reducing bias. See bias, avoiding	and randomization, 243-44



More Information

safety variables, 178	more than one group, 67 66-68
and blinding, 266–67	for rare disease with uniformly poor
ethical issues, 185	outcome, 65
in interventional study 179	with sequential groups, 65-66
in observational study, 181-82	single-blind study, 262-64. See also blinding
sample size, 390-401	speakers of foreign languages
alternative way of thinking about, 398-99	and informed consent, 35, 40, 148
calculating, 391-92	and questionnaires, 347-48
effect size, 392	recruitment of, 168
ethical issues, 400-01	special populations
importance of, 390-91	and informed consent, 38-41
"just right" number for	children, 35, 38-39
calculating, 391-92	persons unable to understand and agree to
clinically important difference, 393-94	study, 39
magical thinking and, 398-99	pregnant women, fetuses, neonates, 31, 40-41
problem with, 393-94	prisoners, 41
ways to decrease, legitimate, 394-97	speakers of other languages, 35, 40
change endpoint, 394-95	recruitment of, 168
decrease power, 397	See also study population
modify statistical characteristics, 397	spreadsheets. See data storage
reduce variability between individuals,	staff, importance of, 168-71, 289
396	"standard" diet, defining, 315
reduce variability of measurements,	Standards for Privacy of Individually
395–96	Identifiable Health Information
key points, 401	(Privacy Rule), 17-18, 24, 298, 372
noise, 392	storage stepped wedge design, 79
ratio of, between different groups, 399-400	statistical significance
variability, 392	vs. clinical importance, 380
scientific validity, as ethical issue, 19–20. See	determining, 383-86
also validity	See also hypothesis testing; sample size
scoring of structured interviews, 349. See also	statistics, 12
raters	validity of, 144
selecting design. See design selection	stepped wedge design, 79
selection bias, 206-08	storage. See data storage
single arm study, 47-48, 64 64-66	stratification, 250–52
clinical trial phase, 53, 65-66	benefits and pitfalls with, 254-55
disadvantages of, 64 64-66	defining study strata, 250-51



418 Index

stratification (cont.)	medical history, 153-54
implementation, 251-52	medications, 149
reasons for, 250	physical examination, 152-53, 155-56
structured interviews	suitability, 238
bias reduced with, 219, 223	individuals actually studied, 157-58
as data collection instrument, 345	key points, 159-60
example of, 150-51, 223	study group, 157-58
scoring of, 349	study pool, 147
and training of assessors, 223-24	See also case-control study, participant
study design, 47-61	identification; cohort study,
ethics and, 59-61	participant identification
key points, 61	superiority study, 63, 71, 379-80
See also design selection; interventional	surrogate variables, 193-95
study; observational study	
Study ID, 246, 343-44, 372	time considerations, 123, 129
study population, 147-60	time-related outcomes, 192-94
ethical issues, 158-59	time to event, 193
coercion of family members to	time trends, 192–93
participate, 159	tissue samples, 41-42
exclusion of subgroups, 158-59	Type I (α) error, 380–81. See also hypothesis
informed consent, 158	testing
screening procedures, order of 159	Type II error(β), 381–82. See also hypothesis
inclusion and exclusion criteria, 148-57	testing
ability to communicate with participant	
as, 157	unbalanced randomization, 255-56
availability for study as, 157	unblinded study, 264-66. See also blinding
in case-control study, 313-16	underreporting of adverse events, 209, 308
in comparative cohort study, 304-05	undue influence, and informed consent, 37–38
contraceptives, 154-55	unequal randomization, 253, 255-56, 399
demographics, 152	United Nations Educational, Scientific and
diagnosis as, 150-52	Cultural Organization (UNESCO), 15
exclusion criteria, 148	United States Public Health Service, 23
common categories of, 149	US Code of Federal Regulations (45 CFR
family history, 154	46.116), 37
inclusion criteria, 148	
common categories of, 149	validity, 143–44
informed consent, 148-49	definition, 137, 143

drop-out rate, 70

lifestyle factors, 156–57



419 Index

ethical issues, 19-20, 145 key points, 146 in multi-site study, 354-55 scientific, as ethical issue, 19-20 and study population, 139-40, 143 See also generalizability variables, 175-86 baseline value of, 176 binary, 175, 190-91 in case-control study, 182 in cohort study, 181 confounding (see predictor and confounding variables) defining, 175 dichotomous, 175, 190-91 ethical issues, 185 field in database, 358 in interventional study, 176-81 key points, 186

measuring, 183–84
in observational study, 181–82
ordered categorical, 175
outcome (*see* outcome variables)
predictor (*see* predictor and confounding variables)
prognostic, 240, 249–50
recoding, 184, 190–92
safety (*see* safety variables)
storing (*see* data storage)
surrogate, 193–95
types of, 175–76
unordered categorical variable, 175–76

women
exclusion from study as ethical issue, 158
and informed consent, 31, 40–41
World Health Organization (WHO), 15, 26
World Medical Association, 15