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Tutor

TutorialsinClinicalResearch:PartIV:

RecognizingandControllingBias

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Objective: This is the fourth of a series of Tutorials in Clinical Research.1–3 The objectives of this article are to heighten reader awareness of biases and of methods to reduce their impact and to provide an easy reference document for the reader during future journal reading. Study Design: Tutorial. Methods: The authors met weekly for 4 months discussing clinical research articles and biases and the secret to brewing the perfect espresso for which they might be at risk. Liberal use of reference texts and specific articles on bias were reviewed. Like the example by Sackett, biases were catalogued to create an easily understood reference. Articles were chosen to demonstrate how understanding bias might facilitate assessment of the validity of medical publications. Results: The article is not organizzed into three main sections. The first section introduces specific biases. Two tables serve as rapid reference tools. The second section describes the most common biases linked to specific research approaches and reviews techniques to minimize them. The last section demonstrates the application of the information to an article in a manner that can be applied to any article. Conclusions: Assessing the validity of a medical publication requires an awareneness of bias for which the research is inherently at risk. A review of the publication to determine what steps the authors did or did not undertake to minimize the impact of biases on their results and conclusions helps establish the validity. This article should be of assistance in this critical review task. Key Words: Bias, confounding factors, research/methods, research design, clinical protocols.
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INTRODUCTION

Biasmeansobliqueorslanted.[4]Biasreferstothe unintentionallyrandomorsystematic,orworse,thewill-

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ful, distortion of truth. In comparative research, each component of the research model (baseline, maneuver, and outcome) must be similar or similarly measured, except for the variable being compared. If the components are not similar, the comparison is slanted, or biased.[5]

Additionally, biases sum to compound the distortion of truth as the research moves along the pathway from the baseline state to ultimate publication and its reading.[6]

Practicing medicine leads to more questions than one can answer; but the important questions must be pursued with efficiency. Understanding what types of studies are required to answer specific questions and how to search for key papers are great places to start. However, to avoid erroneous conclusions, the papers found must be evaluated for validity.

A rapid means of assessing validity begins by antic-ipating specific biases that might influence the results and by determining if the authors acknowledged and at-tempted to control these biases in the design, conduct, and analysis of their work. The significance of bias lies in its erosion of validity of data and conclusions; in turn this promotes falsehoods as reality, which if applied to patients, may inadvertently endanger them.

Each of the major parts of an investigation are at risk of bias, including selection of subjects, performance of the maneuver, measurement of the outcome, data collection, data analysis, data interpretation, and even reporting the findings.

The purpose of this article is to assist the busy practitioner in identifying common types of biases and the methods used to minimize them.

BIASES COMMON IN CLINICAL RESEARCH

It is worth emphasizing that the control of bias is a lifelong, progressive endeavor and that the literature describing methods to minimize biases abounds.[5] However, a brief awareness of specific biases and counter measures to control for them is helpful.

Many types of biases have been described and several names may label the same type of bias among different authors. To facilitate understanding of the different types of biases, it is helpful to progress through the research process (literature review, baseline state, maneuver, out-

come,analysis,publication);eachcomponentissuscepti-bletotheinadvertentinfluenceofbiases.Theclassic paperbySackettwasusedasamodelforthefollowing section.[7]

Publication,LiteratureReview,orResearching theTopicBiases

Reading the literature about a topic may promote an opinionthathasarisenundertheinfluenceofseveral possiblebiases.With*abiasofrhetoric*,theconclusions may be based on opinion rather than evidence. A *one-sided referencebias*mayoccurwhenanauthorrestrictshis referencestopapersthatsupporthisopinions,thusthe reader ends up with a skewed understanding of the topic. A *positive results bias* slants opinions because authors and editorsarelesslikelytopresentorpublishnegativere-sults(TableIA).

These are just some of the ways readers may obtain a slantedopinionaboutaspecificdiagnosticprocedure, treatment,orothercomponentinmedicalpractice.

SelectionorSusceptibilityBiases

Selectionbiasesarealsocalledsusceptibilitybiases. These occur when the groups to be compared are differen-tiallysusceptibletotheoutcomeofinterest,evenbefore theexperimentalmaneuverisperformed.Theresultant dissimilaritiesinthebaselineattributesmayinfluence theoutcomeindependentoftheexperimentalmaneuver. For example, *popularity bias, centripetal bias*, and *referral bias* may skew the sample population in certain practices orcenterssothatthesesubjectsmightbedifferentfrom thegeneralpopulationseeninotheroffices.

Selectionbiasesareperhapsoneofthemostimpor-tant groups of biases. Multiple potential biases may occur atthispoint.SeeTableIBforthelistofthesebiases capableofinfluencingsubjectselection(TableIB).

ExposureorPerformanceBiases

Exposurebiasesarealsocalledperformancebiases. Thesebiasesrefertothosethatrelatetoexposuresthat are suspect of causing disease or interventions that might have an effect on disease. For example, in *proficiency* bias, theproficiencyofthesurgeonscouldbiastheresults.If treatmentAwasdonebyagroupofskilled,experienced surgeonsandtreatmentBwasperformedbyjuniorresi-dents,abiasinthecomparisonoftreatmentsmightbe expected.Poorpatientcompliance,*compliancebias*,can yieldresultsthatarenottheresultoftheintervention; however, subjects randomized to this treatment arm must becountedashavingthetreatment.Greatcaremustbe taken in the design of the project to determine compliance andtoinsurecomplianceisgood.*Withdrawalbias*isa serious problem. If subjects withdraw or are lost from the study, there is no way to know what would have happened tothem;itcannotbeassumedthattheywillrespondlike thosewhostayedinthestudy.Awell-designedandexe-cuted study will expend great effort to select reliable sub-jectsandkeeptrackofallsubjects.TableICliststaddi-tionalexposure/performancebiases(TableIC).

DetectionorMeasurementBiases

Detectionbiasesarealsolabeledmeasurementbiases.Biasinmeasurementofoutcomesisacommonand seriousproblem.Likeselectionofsubjects,thisgroupof biasesisimportant.

Becauseofstrongpropensityof*expectationbias*,if the treating or intervention physician is also the one measuringtheoutcome,biasisalmostassured.Itiscrucial that the outcome assessor is unaware of the intervention; itisalsohelpfulthattheybeblindedtothehypothesis understudyandconcentrateonlyonmeasuringtheoutcomeparameter(s)ofinterest.Someofthesebiasesare reduced by the technique of double-blinding, meaning that both the subject and the treating physician are not aware oftheintervention;inanycase,itiscrucialthatthe outcome assessor is blinded. The list in Table ID itemizes anumberofwaystheoutcomemeasurementteamor personcanbebiased(TableID).

AnalysisorTransferBiases

Analysisbiaseshavebeencalledtransferbiases.[5] Aftertheimplementationandcompletionoftheinvestigation,theresultsmustbecomparedandanalyzedfor significance.Transferringthedataintoanorganized structureforthatanalysiscreatesopportunitiesforbi-ases. *Data dredging bias*, searching through the data look-ing for anything that might account for differences or that mightcorrelatewithsomething,and*tidying-upbias*,ex-cluding data points because they do not seem right, are all toocommon.An*apriori*designthatincludesdefinitions, hypotheses,andanalysestobedoneiscrucialforavalid study(TableIE).

InterpretationBiases

Followingdataanalysis,aninterpretationofthere-sults is typically offered. This represents yet another step in which biases can skew results away from the truth. For example,*cognitivedissonancebias*isalltoocommonin theliterature.Inthisbias,theinvestigatorisconvinced thatatreatment,pathophysiology,diagnosticprocedure, orotherareaofinterestisbetterorworse,true,ornot true, and despite findings to the contrary, will steadfastly contendthathisorherpointisstillvalid.Thisisoften seenwhenaninadequatestudyconcludeswithadmonitionsfortreatmentordiagnosticmaneuversthatare wholly unsupported by the results. All of the biases listed inTableIFareeasilyseeninthemonthlyliterature offerings(TableIF).

PublicationBiases

Theprocessiscomplete,exceptforpresentingand publishing the data. This too has inherent biases because authorsarelesslikelytosubmitnegativeresultsand editorsarealsounlikelytopublishthem.Thesebiases, seeninTableIA,applytotheprocessofpresentingand publishingtheworkandinreadingtheliteratureafter publication,asmentionedabove(TableIA).

Confounding

In the prospective studies, such as clinical trials (randomizedornonrandomized)andprospectivecohortstud-

(Continues)

Themeasuredefficacyofatreatmentcanbeconfoundedbynon-adherencetotheregimen

Subjectsthatdropoutmaydiffersignificantlyfrom thosethatremain

Thecontrolgroupsubjectsmaymistakenlyreceivethemaneuverofinterestorbeaffectedbyanextrinsicmaneuver,whichdiminishesthedifferencesinoutcomesoftheexperimen

ExposureBias(performancebias)

Inabilitytoobtainauthorizationforreleaseofmedicalrecordsfrom somesubjectsmaynotbeofferedatreatmentbecauseofcoexistingmorbidities orpoorprognosis

Somesubjectsmaybeparticularlyresistanttoorloverlysusceptibletoanexperimentalmaneuver

Nonrandom assignmenttoasspecificstudygroupbasedonprognosticvariablescancreateincomparablegroups

Volunteersubjectsthatdifferfrom thebroadertargetpopulationwithrespecttoexposures ,diseasestatus ,comorbidities ,etc

Thegroupwhofailstorespondtoasurveymaynotreflectthentirepopulationsurveyed

Participationinagroupmayimplyalevelofhealththatisdifferentfrom thegeneralpopulation ,i.e.,constructionworkersorrunners

Migrantsmaydifferfrom thepopulationaswholewithrespecttotheirsusceptibility todisease ,procurementofhealthcare ,andavailabilityforfollow-up

Socallyunacceptableconditionstendtobeunderreported

Failingtoidentifythestartofexposureordiseasemayleadtoerrantstratification

Overtime ,changesindefinitions(including staging),exposures ,diagnosticabilities ,andtreatmentsmayormaynotbeofferedatreatmentbecauseofcoexistingmorbidities orpoorprognosis

Clinicaldatamightbemissingyetconsiderednormalwhenitisnegativeornotascertained

Patientsmayormaynotbeofferedatreatmentbecauseofcoexistingmorbidities orpoorprognosis

Whengroupsbecomeverysspecificallydefinedtheymaynotberepresentativeofthebroaderpopulation

Thesameconditionmaybeknownbymultiplemonikerswhichifunknowncouldimpacttheacquisitionofsubjects

Thelatelookatthepre-valenceofadiseaseinapopulationmayunderestimatethepre-valencebecauseoffatal ,mild ,orresolvedcases

Therelativefrequencyofadiseaseinhospitalizedpatientsmaynotreflectthefrequencyofthepopulationaswholeandthusmaybiasthestudy

Toosmallasamplemightmissasignificantdifferenceswhiletoolargeasamplemightestablishsignificantdifferencesthatarenotclinicallyrelevant

Knowledgeofpre-existingevaluationresultsmightalterthesubsequentdiagnosticprocessonthesamepatientorhisrelatives

Aninnocentexposureiserrantlyconsideredcausativewhenitproducesasimilarbutunrelatedcondition ,whichismistakenforthediseaseofinterest

Signsorsymptomssometimesassociatedwithacertaindiseasemaybecausedbyaninnocentexposure ,whichresultsinanunusualsearchforthedisease

Knowledgeofapre-existingexposuremayinfluencetheintensitywithwhichthediagnosticprocessisapplied

Peoplevaryintheirabilitytoprocurediagnostictestingwhichestablishesthepresenceofagivendisease

Referralofdifficultcasestotertiarycentersincreasestheconcentrationofraredisordersinthecenter’spatientmix

Therepu tationofaclinicianorcentermaydrawindividualswithspecificdisorderstothem skewingtheirpopulation

Heightenedinterestinacondition mayattractpatientstoaspecificcenterwhentheywouldn’totherwisepresentforinclusion

SelectionBias(susceptibilitybias)

Meta-analysesbasedonlyonpublishedmanuscriptsmissunpublishedpossiblyrelevantstudieswhichmaymisleadtheconclusions

Fundingsourcesmayinfluencetheprobabilityspecificresultsgetpublished

Publishedresultsareextrapolatedtoadifferentpopulation

Errantresearchpreviouslypublishedmaybeusedtosupportaparticularinvestigation

Topicsreceivingunusuallevelsofattentionmaytempt authorsoreditorstorushadditionalresultstopublicationregardlessofthequalityofwork

Investigatorsandpublishersaremorelikelytosubmitandacceptmanuscriptswithpositiveresults

Authorsmaycitemorereferencesthatsupporttheirpositionthancontradictit ;thisservestoskewtheunderstandingofthetopic

Biasagainstcontroversy;publicationsmayexcludeorplaydownreportswhicharecontentious

Falsiousargumentspresentedinacompellingmannerbutwithoutappealingtoreason :theconclusionsareoftenbasedonopinionratherthanevidence

PublicationBias(researching thetopic)

Definition

ListofBiasesandDefinitions .*

TABLE1 .

Named Biases	A	B	C
			tal and control groups
	1. Bias of rhetoric	1. Popularity bias	1. Contamination bias
	2. All's well literature bias	2. Centripetal bias	2. Withdrawal bias
	3. Reference bias[4]	3. Referral filter bias	3. Compliance bias
	4. Positive results bias[5]	4. Diagnostic access bias	
	5. Hot stuff bias	5. Diagnostic suspicion bias	
	6. Pre-publication bias[16]	6. Unmasking bias	
	7. Post-publication bias[16]	7. Mimicry bias	
	8. Sponsorship bias[7]	8. Previous opinion bias	
	9. Meta analysis bias[7]	9. Wrong sample size bias	
		10. Admission rate bias (Berkson)[18]	
		11. Prevalence-incidence bias (Neyman)[7]	
		12. Diagnostic vogue bias[7]	
		13. Diagnostic purity bias[7]	
		14. Procedure selection bias[7]	
		15. Missing clinical data bias[7]	
		16. Non-contemporaneous control bias[7]	
		17. Starting time bias[7]	
		18. Unacceptable disease bias[7]	
		19. Migrator bias[7]	
		20. Membership bias[7]	
		21. Nonrespondent bias[7]	
		22. Volunteer bias[8]	
		23. Allocation bias[5]	
		24. Vulnerability bias[5]	
		25. Authorization bias[19]	

TABLE I.

(Continued.*)

Definition

Unblinded treatment allows the practitioner to influence the patient's perception of benefit

When subjects allocated to the experimental maneuver group expire or withdraw before the maneuver is administered and are reallocated to the control group or are omit

Subjects may be mislabeled and subsequently be allocated to the wrong group for proper comparison

Experimental maneuvers or treatments may not be equally administered to subjects

D Detection Bias (measurement bias)

The outcome measure may not be capable of detecting clinically significant differences

Cases subjects may more intensely review prior events or exposures searching for a cause, thus different levels of recall of exposures may occur compared with control

The natural tendency to convert analogue data to digital data using a preferred ending digit; for example, an even digit rather than an odd digit

Certain measures can be artificially affected by interaction with investigators, e.g., blood pressure in epistaxis patients

Measurements themselves can be painful, intrusive, or embarrassing, resulting in avoidance

Subjects may alter their response toward the direction they perceive desired by the investigator

Observers may err in measuring data toward the expected outcome, e.g., normal temperatures in postoperative patients with fever

The substitution of a risk factor that has not been established as causative may broaden the study population inappropriately

Family communication regarding exposures or illness is stimulated by a case subject in its midst; thus more intense remembrance may occur compared with control subjects

Knowledge of a subject's disease status may affect the intensity of a search for the cause

Cases may be questioned about exposures more vigorously than control subjects intensifying their recollections

Subjects may alter their behavior when they know they are under scrutiny, thereby altering outcomes

Calibration errors may lead to inaccurate measurements being recorded, e.g., an unbalanced weight scale

When a new treatment is under study, the subjects may be monitored with greater scrutiny than control subjects to guard against adverse reactions

Diagnostic procedures investigating a sign or symptom may discover an unrelated previously undetected disease which is then falsely associated with the original sig

The maneuver of interest is not well-delineated so unwitting, inadvertent exposures that effect the maneuver might occur, e.g., measuring blood glucose times without identifying

If testing the efficacy of a diagnostic process is restricted only to patients proven to have the disease, the sensitivity of the test can be overestimat

E Analysis Bias (Transfer Bias)

Levels of significance determined after data collection may lead to errant conclusions

Data reviewed for any and all possible associations without a predetermined hypothesis may yield faulty conclusions

Collapsing of measurement scales may obscure differences; for example, collapsing dimensional data, such as specific age, into ranges, such as 0–40, 41–80, etc., may mi

Excluding outlying data that seems implausible cannot be statistically justified and contaminates the analysis

Repetitive analysis of the accumulating data may lead to premature conclusions and inappropriate termination of the trial

F Interpretation Bias

Efforts to improve patient compliance in a trial may instead cause the investigator to manage more aggressively, or determining treatment outcome it may be errantly attri

Belief in a hypothetical mechanism may increase, rather than diminish, in response to contradictory evidence; for example, a subject or physician may believe more

Interpretation of data may be affected by the way the data is presented, using measurement scales that create a preferred illusion biases the interpretation; for exam

Confusing statistical significance with clinical significance may result in pointless conclusions

Equating a correlation with causation risks making fallacious conclusions; for example, histological membranous ectasia (hydrops) seems to be correlated with symptoms

Failure to reject the null hypothesis because of a limited investigation may lead to authoritarian speculation rather than truthful conclusions

* The general organization and many of the named biases were taken from the classic article by Sackett.

prevent goal and hearing loss. but is not synonymous with necessarily causative

Pe, an increase of 10 000 may actually represent only an increase of 0 001 %

strongly than even in antibiotics for a viral sore throat despite strong proof to the contrary

but ed to the original prescribed treatment

simportant relationships

ed

for the subject's products that commonly contain aspirin

nor symptom. e. g. CT or MRI imaging for evaluation of headache disclosers an asymptomatic maxillary sinus mucus retention cyst

ed the experimental and control groups are no longer matched and the difference between may be biased toward the experimental group

subjects

Named Biases

4. Therapeutic personality bias[7]

5. Bogus control bias[7]

6. Misclassification bias[8]

7. Proficiency bias[5]

1. Insensitive measure bias[7]

2. Underlying cause bias (rumination bias)[7]

3. End-digit preference bias[7]

4. Apprehension bias[7]

5. Unacceptability bias[7]

6. Obsequiousness bias[7]

7. Expectation bias[7]

8. Substitution game bias[7]

9. Family information bias[7]

10. Exposure suspicion bias[7]

11. Recall bias[7]

12. Attention bias[7]

13. instrument bias[7]

14. Surveillance bias[5]

15. Comorbidity bias[5]

16. Nonspecification bias[5]

17. Verification bias[20] (work-up bias (deliberate

5. Repeated peek bias[7]

4. Tidying-up bias (deliberate

3. Scale degradation bias[7]

2. Data dredging bias[7]

1. Post-hoc significance bias[7]

6. Under-exhaustion bias[7]

5. Correlation bias[7]

4. Significance bias[7]

3. Magnitude bias[7]

2. Cognitive dissonance bias[7]

1. Mistaken identity bias[7]

bias)

elimination bias)

ies, innate distortions, i.e., biases, are generally located in andeffectspecificsitesalongtheresearchpathway.As mentionedabove,thesebiasesarebroadlynamedforthe siteinwhichtheyoccur;forexample,inappropriatead-missionbias,susceptibilitybias,performancebias,detec-tionbias,andtransferbias.However,inretrospective studies,suchasretrospectivecohortstudiesandcase-

group,thesestudiesguardagainstbiasesthreateninga study's validity.[8]Yet despite these techniques, some types ofbiasmaystillimpactRCTs.Risksevenexistafterthe experiment is complete during data analysis and interpre-

controlstudies,somebiasesmaybehardertonameand identify. Some of these biases are external to the pathway and may affect both the maneuver and the outcome. These biasesarecalledconfoundingvariables,orconfounders. Becausethesearevagueindefinitionandlocation,the investigatormustperform"areviewofsystems"onthe research pathway for the specific project to search for any additionalvariablesthatmightdistortthetruerelation-shipbetweentheexposure(maneuver)andtheoutcome.[5] Theseconfoundingvariablesareextraneoustothe researchdesign,butmayinterferewiththeassociation betweentheexposureandtheoutcome.Aconfounding variable:1)isassociatedwiththeexposure;2)although independentoftheexposure,itisariskfactorforthe disease,sometimesinanoccultorpreviouslyunrecog-nized way; and 3) is not a direct link between the exposure andthedisease.Forexample,ifexposuretoAisbeing investigatedtodetermineifitcausesdiseaseB,however olderpeoplearemuchlessexposedtoAbutaremuch morepronetogetdiseaseB,agemaybeconsidereda confounder.Ifthestudydoesnotcontrolforage,the confounder,exposuretoAmaybefalselyassumedtobe thecauseofdiseaseB.[8]

BIASES LINKED TO SPECIFIC RESEARCH TECHNIQUES

Thedifferenttypesofresearchapproachescanbe arrangedinahierarchicalorder,whichisbasedonthe easeinwhichbiasesareminimizedbythestructural approachperse.Inthisarrangement,therandomized, controlled trial is considered the least subject to bias. It is followedbythecohortstudyandfinallythecase-control study.All,however,aresubjecttoseriousbiases.

The first step to minimize bias is to have a clear idea ofthequestion,andwhatapproachisrequiredandfeasi-bletoachievetheanswer.Thesecondstepistoprospec-tivelydesignthestudyindetailbefore,or*a priori*,the investigationisundertaken.

AshasbeenmentionedinthepprecedingTutorials, evensearchingtheliteratureisbestdonewithaclear questioninmind,aprospectivelydesignedapproachfor thesearch,andaclearideaofthespecificresearchap-proachrequiredtoanswerthequestion.Thisprospective approachtoliteraturesearchingimmediatelyhelpsmini-mizesuccumbingtothepublication,literaturereview, researchingthetopicbiases.[9]

RandomizedClinicalTrials

Arandomizedclinicaltrial(RCT)isusuallythebest approachtodetermineanewtreatmentefficacyand safety. It prospectively compares effects of a new interven-tional maneuver on the experimental group with a placebo orstandardtreatmentonthecontrolgroup.Byusing tation.Biasismorelikelytooccuratthisjunctureifthe hypothesishasnotbeengenerated*a priori*oriftheconclusionsextendbeyondthequestionaddressedinthe hypothesis.

An example demonstrating the strengths of the RCT is the article "Bells Palsy Treatment with Acyclovir and Prednisone Compared With Prednisone Alone: A Double-Blind, Randomized Controlled Trial."[10] After reading the article, it is obvious that selection bias, execution of the treatment, and measuring its outcome have been man-aged to a degree by using a control group, randomization, and double blinding. Blinding examiners minimized bias in detection. Finally, the authors' conclusion cites the findings of the study. In summary, the authors applied a regimen to minimize bias and made evidence-based conclusions, successfully minimizing some of the obvious biases that might have seriously threatened the validity of their study. This is not to infer that this is a perfect example, but it is a reasonable one for this survey.

Cohort Studies

A cohort study, by definition always prospective unless otherwise stated, follows one or more groups forward over a period of time. The purpose is often to identify exposures occurring in subjects that might result in a specific outcome of interest. By noting a temporal sequence between exposure and outcome, inferences about causation can be made.

A cohort study reduces bias relative to assessing the potential cause(s) of a disease because the outcome (dis-
strategies like randomization, blinding, and a control ease status) is unknown to the examiner at the time of exposure documentation. However, during attempts to look retrospectively at the same question of cause by look-ing at medical records in a retrospective cohort, this pro-tection may be lost unless the exposure examiner is blinded to the outcome.

Significant biases may effect cohort studies, includ-ing sampling, measurement, data analysis, and interpre-tation biases. These may be minimized by selecting a sample of subjects that is representative of the larger population at risk of the disease and by selecting a control group, which will not receive the exposure in question but is similar in all other factors. Unbiased and appropriate selection of these comparison groups is difficult. Addition-ally, limiting attrition of subjects is essential, as is the *a priori* hypothesis regarding the relationship between ex-posure and outcome.

An example of a cohort study with some good bias control and bias errors can be found in "Development of Tympanosclerosis in Children With Otitis Media With Effusion and Ventilation Tubes."[11]

The cohort reflects the at-risk target population: young children with otitis media with effusion. The inves-tigators established an effectively matched control group of ears by only treating one ear; all the subjects had bilateral effusions. Through careful selection, bias at this step was avoided.

Thereafter, however, the study was subject to a numberofbiasesindetection,dataanalysis,interpretation, and publication. The observers were not blinded to at least thehypothesisandthemeasurementofdegreeoftympanosclerosiswassubjective.Dataanalysisbecamedifficult tofollowafterthefirstsetoftubes.Bytheendofthe 5-yearstudy,37.8%ofsubjectshadwithdrawnorwere losttofollow-up;nostatementsaccountingforthemwere offered and their missing evaluations were not considered in the data analysis. The interpretation of data suggested severalbiasesintheDiscussionsection.Forexample,"it seems that tube insertion on only one occasion can induce changeswhichareassevereasthosecausedbyinsertion oftubesonseveraloccasions."Nosuchcomparisonwas madeinthepaper,sonosuchinferencecanbemade. Anotherexampleofbiasedinterpretationsuggestedcognitivedissonancebias."Althoughfromthisstudy,tube reinsertion may not significantly affect the development of tympanosclerosis,theinsertionmayincreasetheother damagetothetympanicmembrane."Theauthorsreinforcedtheirpositionevenintheфaceofcontradictoryor missingevidence.

In deference to the authors, this is a difficult study to doinanunbiasedmanner;however,withatightdesign, suchastudycouldbevalid.

Thepurposeofthisexampleistoillustratesomeof the subtle but important biases that can occur during the conduct of a study and during the reading of the literature toanswerquestions.

Case-ControlStudies

A case-control study identifies two groups of subjects whoaresimilarbutdifferwithrespecttothepresenceor absenceofaparticulardisorder.Caseshavethedisorder andcontrolsdonot.Thenalookatcharacteristicsor exposuresisundertakentoseeifthetwogroupsdifferby someputativecauseofthedisorder.Thisallowsinfer-ences about a possible relationship between exposure and outcome.

This method of study is prone to many sources of bias andislessabletodefendagainstthem,yetoffersapracticalmeansofansweringmanyclinicalquestions.The potentialbiasesincludeselectionbias,observationbias, and biases from analyzing and interpreting the data. The selectionofthecontrolsisparticularlysubjecttosubtle, butimportantbiases.Biascanbeminimizedbycarefully matchingcontrolstocases,applyingtheappropriateobservational technique identically to both groups, and gathering information from both groups in the same fashion. A carefulevaluationforpotentialconfoundingvariablesis important.

Anexampleofacase-controlstudyisdemonstrated in"PharyngealpHMonitoringinPatientsWithPosterior Laryngitis."[12]Thecasesconsistedofconsecutivepatients diagnosed with posterior laryngitis after suggestive symptomswerenotedandconfirmatoryphysicalfindingswere seenonvideostroboscopy.Healthyage-matchedvolunteerswererecruitedbyadvertisementandwerefreeof anyrefluxsymptomsorsigns.

Bothgroupswereexaminedbypharyngoesophageal pHmonitoring.Bymatchingcontrolswithcases,andby

eliminatingfromcontrolsanyonewithrefluxsymptoms on a questionnaire, the authors minimize selection biases fromthisstudy,iftheissuewastodifferentiatebetween asymptomaticnormalsubjectsfromthecasesandifthe questionnairewasvalidatedforthatpurpose.Onthe otherhand,iftheissueweretodifferentiatepeoplewith symptoms,butwithoutobjectiveevidenceoflaryngitis, thisstrategywouldnotwork.

Datarecordedinbothgroupsincludedp Hexposure inthepharynx,proximalanddistalesophagus.Analysis ofthedatawasperformedonlyonp Hmeasurestodeter-minestatisticalsignificance.Conclusionswerethenlim-itedtooriginalobjectivesforwhichevidencehadbeen collected,therebyminimizinginterpretationbias.

In summary, the investigators established an *a priori* question,collectedinformationinidenticalfashionfrom cases and controls, and drew specific conclusions based on their data. This is not a perfect example; however, it does servetoillustratesomeofthemethodstoreducebiases.

METHODS TO MINIMIZE THE IMPACT OF BIASES ON RESEARCH

Alistofsomeofthespecificmethodstoavoidor minimizebiasisdisplayedinTableII.

Searchingforbothpositiveandnegativepublished studies and trial registries for unpublished investigations canhelpreduce*publicationbiases*.

Using strict eligibility, inclusion, and exclusion crite-ria and randomization for the allocation of maneuvers can minimize*selectionbiases*.

*Exposurebiases*arediminishedbyprospectivelyes-tablishingcriteriaforperformingtheexperimentalma-neuverandblindingtheinvestigatorandsubjectswhen possible.Rigorousmaintenanceofcontactwithsubjects helpstoavoidnoncompliance,withdrawal,andlossto follow-upfromthestudy.

*Measurementbiases*canbereducedbyprospectively establishing detailed methods for data collection, by blind-inginterviewerstosubjects'diagnoses,orbysolicitinga historyofexposurebeforeadiagnosisisdetermined,and byapplyingdetectionmethodsequallytobothgroups. Additionally,itishelpfultoseekexposureinformation fromindependentsources.[7] Requiringresponserates of over80%canminimize*nonrespondentbias*.Matchingas many confounding variables in cases and controls in case-controlstudieshelpsminimizebiasesaffectingtheinter-pretationofputativecausalexposures.

Analysis biases are decreased by prospectively choos-ingstatisticalmethodsbestsuitedtoevaluatethedata andanalyzingtheassociationbetweenconfoundingvari-ablesandtheresults.

*Interpretationbiases*canbeavoidedbyusingoneor morecontrolgroupsandbybasingconclusionsonthe hypothesis-drivendatacollection.

ExampleArticleforBiasAssessment

Commonexamplesincludethelatestnewscitedby thepress,themonthlyjournalsthatarriveonourdesks, ortheartic leshandedoutbypharmaceuticalrepresenta-tivessupportingtheirproducts.

TABLEII.
CategoriesofBiasandTechniquesforControl.

CategoryofBias	ControlTechniques
APublicationBias	
	Establishsimilarnumbersofpositiveandnegativepublishedstudies[17]
	Investigatorsshouldpresentnegativestudiesforpublicationandeditorsshouldpublishnegativestudies[17]
	Evaluatevalidityofstudiesbasedontheirmethodsnottheirconclusions;thenweighttheirconclusionsaccordingly[17]
	Searchtrialregistriesforunpublisheddata[17]
	Identifyfundingsourcesandpossibleconflictsofinterest
BSelectionBias	
	Selectthemostrigorousstudydesignfeasibletoaddressthehypothesis[5,8]
	*Apriori*createexplicitcriteriadefiningmethodstobeusedthroughoutthestudy[5,8]
	Randomizationremoveshumanjudgmentfromallocationtothegroupsandshouldbeusedwheneverpossible[5,8]
	Createspecificcriteriaforadmissiontoevaluatethemaneuver[5]
	Ascertainsubjects'baselinestateandclassifythembasedonthatstate[5]
	Controlgroupsshouldbesimilartotheexperimentalgroupwithrespecttovariablesthatarepredictorsofdisease incidence[21]
	Incase-controlstudiesbothgroupsshouldonlybecomprisedofsubjectswhohaveundergoneidenticaldiagnostic testingandthereshouldbenodifferenceinhowexposureordiseaseinformationisgathered[8,7,20]
	Createalistofallpossiblemeansofexposuretothemaneuverofinterestpriortotheperformanceofthemaneuver, andthenscreensubjectsfortheseexternalexposures[5]
	Matchoradjustforconfoundingvariablesinthetwogroups[20,7]
	Morethanonecontrolgroupcanbeestablished[21]
CExposureBias	
	Selectthemostrigorousstudydesignpossibletoaddressthequestion[5]
	*Apriori*establishspecificcriteriaforperformingthemaneuver[5,7]
	Blindingusedinexperimentaltrialspreventsknowledgeofthemaneuversfrominfluencingtheoutcome measurement[5,8]
	Hidethehypothesisfromtheinterviewerandsubjects[5]
	Considercreatingdecoyhypothesestodisguisethequestionofinterest[5]
	Divide the labor, i.e., someone other than the person to ascertain the outcomes must performance of the maneuver[5,8]
	Maintainaggressivecontactwithsubjectstomaintaincompliancewiththeprotocolandtominimizeattritionfrom the study[8,7]
DDetectionBias	
	*Apriori*establishexplicitcriteriaforcollectingdataonexposuresandoutcomes[7]
	Limitanydifferencesbetweengroupsinhowinformationisobtainedaboutexposure,disease,oroutcome[8]
	Doubleblindingsubjectsandinvestigatorswhenpossiblepreventsknowledgeofexposuresfrominfluencingthe detectionofoutcomeevents[5,7]
	Blindtheinterviewertothehypothesis[5]
	Establishrigorous,rigid,formatfordataacquisition,i.e.,phrasingofquestions,methodsforrecordinganswers,etc[5]
	Detectionproceduresshouldbeappliedequallytobothgroups[5]
	Hidetheidentityofthesubjectsfromthedatacollectorwhenpossible[5]
	Usearchiveddata[5]
	Acquiredataaboutexposurefromindependentsources[7]
	Createadivisionoflaborbyhavingadifferentpersonrecorddatathanperformsthemaneuver[5,8]
	Examineforpotentialconfoundingvariablesaffectingtheoutcome[8]
	Maintainaggressivecontacttoavoidattritionfromthestudy[8]
	Forquestionnaires,obtainresponseratesof!80%[7]
E AnalysisBias	
	Establish*apriori*thestatisticalmethodsbestsuitedtoevaluatethedata[5,8]
	Donotuseunknowndata,butdoreporthowitwasmanaged[5]
	Determinethesignificanceoftheassociationbetweenconfoundingvariablesandexposuresandoutcomes[8]
	Donotexcludeoutlyingdifficulttoexplaindata[7]
F Interpretation Bias	
	Usecontrolgroupsforcomparison[8]
	Baseconclusionsonthedataandlimitthemtothehypothesis[5]

Recentlyapharmaceuticalrepresentativedelivered thearticle“OnsetofActionandEfficacyofTerfenadine, Astemizole,Cetirizine,andLoratadinefortheReliefof SymptomsofAllergicRhinitis.”[13]Thisarticlewasanat-tractive example to use in this manuscript because it was unsolicited, came from a journal outside of otolaryngology, andyetwasgermanetomostotolaryngologists.Thefor-mat used to discuss this example article was to emphasize the positive aspects of the study design and study conduct, and to illustrate the measures to control biases. It was not theintentiontoformallycritiquethework.

A systematic approach to assess the authors' attention toandcontrolofbiasesbeginswiththestatedresearch question. They proposed to compare onset and efficacy of the medications.Aquicklookatthemenuofresearchap-proachestobestanswerclinicalquestionsandsomereflec-tion on the feasibility of studying this question suggests that a randomized, double-blind, placebo-controlled design would be best.[3]The authors did use this design.

Therandomizeddesignspecificallyattemptedto makethegroupscomparablebyhopingtorandomlydis-tributeallofthebaselinevariablesequallybetween groups, thus helping control for *selection bias*. Sometimes even randomization fails to make the groups exactly alike. Analyzing the baseline variables between groups to deter-mine if significant differences were found could check this; TableIinanarticleisoftendevotedtothisexercise.In this article, Table III assessed some of these variables and foundnosignificantdifferences.

Double blinding, meaning the subjects and the inves-tigatorwereunawareor“blinded”totheinterventional maneuver,helpscontrol*detectionbias*.Thisminimizes thenaturaltendencyofthesubjectsandoftheinvestiga-tor to skew results toward some preconceived “better med-icine.”Becauseneitherknows,itgiveseachmedication andtheplaceboanequalchancetorelievesymptoms,if indeedtheydo.Theydidthis.

Theplacebocontrolwasanimportantwayofdeter-mining if any of the medications were more effective than nomedication.Thishelpedavoid*therapeuticpersonality bias,expectationbias,*and*measurementbiases*.

Another appropriate early question is did the funding source influence the results? Were there conflicts of inter-est?Thiscouldnotbeclearlydetermined.

Havingascertainedthesedesignissuesquicklyfrom theMaterialsandMethodssectionofthearticle,greater scrutinyrevealedadditionaleffortstominimizebiases.

Theselectionprocessisahigh-riskendeavorthere-foreattentionwasfocusedthere.Didtheauthors*apriori* definetheselectionmethod?Wasthatselectionmethod uniformly applied? In the example, subjects were solicited fromallergicpatientsandbyadvertisement.Thispoten-tiallyriskeda*volunteerbias*,inwhichthestudysample mightdifferfromnon-volunteersorthepopulationat large. This was dealt with by confirming the subjects were representativeofthelargertargetpopulation.Inthis case, eligible subjects were required to have a documented clinicalhistoryofseasonalallergicrhinitisfortheprevi-ous2years,positiveskinteststoragweedantigen,and response to pre-study priming exposure to ragweed pollen

thesecurityoftheexposureroomreduced*contamination bias*.

Executing the experimental maneuvers was the next step in the research method and, of course, the next point in which biases may have had impact. Critical information centersonwhetherthedifferentmaneuverswereapplied inidenticalfashiontoeachgroupunderinvestigation.In theexamplestudy,eachgroupwasadministeredthetest drugaftera1-hourinductionofsymptomsbyragweed pollen in the experiment room. In each group, the maneuverswereadministeredinidenticalfashion.Thishelped control*exposurebias*.

Of111primarysubjects,19didnotcompletethe study. All were accounted for in the Results section where it was noted that 14 left for nonmedical reasons and 5 quit secondarytosymptomsthatweretoointolerabletocon-tinue. However, the impact of this loss on each of the final groupswasnotwelldelineated,increasingtheriskthat *withdrawalbias*mayhavesomeopportunitytoskewthe results.

Measuringoutcomesisalsoatriskforbiases.Inthe example,thesubjectshadtoratetheirsymptomsand response to treatment. This could introduce *attention bias (Hawthorne effect)* and *confounding bias* from intersubject variabilityininterpretingtheseverityofsymptomsand thedegreeofresponsetotreatment.Theauthorsdidat-tempt to minimize the impact by "educating subjects as to standardizedmethodsofscoringseveritylevels."These severitylevelsweredetermined*apriori*,seemedtobe sufficiently sensitive, and seemed appropriate to the study inaventilation-controlledroom.Exclusioncriteriaand question;however,nomentionwasmadeofpreviousvalidationofthescoringmodel.

Analysisofthedataposedthenextthreatfrombiases.Theanalysisshouldbeprospectivelydesignedand hypothesis-driventoavoid*datadredgingbias*.Theauthorsdefinedinadvancethelevelofstatisticalsignificance,therequiredpower,andthestatisticaltestsbeing used in the hypothesis-drivenstudy.

Finally,interpretingthedataalsoissusceptibleto biases. In the Discussion section of the article, the efficacy oftheantihistamineswasranked,basedonstatistically significantdata.Thearticleimpliedclinicallysignificant differences, which was not fully defined by this study; this maybeanexampleof*significancebias*.

Theveryactofpublicationitselfhassomeinherent potentialforbiases,suchas*positiveresultsbias*.The authorsdidnotstatewhethertheywouldhavepublished negativeresultsalone.However,totheircredit,theydid emphasizebothstatisticallysignificantandnonsignifi-cantdata.

CONCLUSION

Clinicalexperienceisderivedfromboththepractice ofmedicineandtheassimilationoftheliterature.That literaturemustbeassessedforvalidityforebeingassimilated;otherwise,itmaypromotemistruthsasreality which,whenappliedtopatients,mayinadvertentlyendangerthem.

Therefore, an awareness of biases and their causations should facilitate their recognition in an article. Uncontrolled biases may render a manuscript invalid.

The text and tables here provide a rapid reference tool for future application by the reader. The example section at the end of the paper illustrates the application of this tool for the validity assessment of an article. The next tutorial will address outcomes research.

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