PHA 6717 - MEASUREMENT IN PHARMACEUTICAL OUTCOMES AND POLICY RESEARCH

Spring 2020
Tuesday, 9AM – 12PM
HPNP 2306

Almut G. Winterstein, RPh, PhD, FISPE & Amie Goodin, PhD, MPP
almut@ufl.edu amie.goodin@ufl.edu

Learning Objectives

- Describe the role of measurement in the context of the scientific method.
- Identify key issues in design and validity of patient-reported outcomes measures, including item and response wording, response scaling, item sequencing, and questionnaire administration.
- Identify data ascertainment techniques, weaknesses and strengths for clinical measures that rely on secondary data sources including billing data, registries, and electronic health records.
- Explain methods of determining reliability, validity and acceptability of measures.
- Define and describe examples of measurement error and misclassification bias in both exposure, confounding and outcome measurement.
- Describe approaches to address measurement error and misclassification bias
- Identify measurement error related to time in making causal inferences
- Assess the impact of measure misspecification and missingness on the ability to find unbiased estimates of an association.

COURSE STRUCTURE AND PROCEDURES

Overview: PHA 6717 is a graduate level class that is structured as a "seminar" or discussion class. The success of such a class depends on your keeping up with the assignments and participating actively in class discussions. As a student in the course, you are also expected to read material beyond the required readings. For example, when the assignment is to read and critique a research article(s), you are expected to thoroughly understand the article. If authors state that they based their research on a validated measure, you are expected to read more to determine whether the measure was appropriately validated and can be used for the research question at hand. If authors state that they used a particular analytic method, you will be expected to read about this method to determine whether or not the method was used appropriately and what its advantages or disadvantages may have been.

Resources posted on Canvas for each week will include an overview of learning objectives, related readings and instructions for a written assignment. Each week some students will be chosen to present the core learning content for that week in class. Those students can choose the mode of presentation they prefer and plan on a succinct 15-30 minute summary in class. The content of this summary should follow closely the learning objectives for the week and synthesize relevant content of the readings as it relates to these objectives. For example, in preparing the synthesis it is important to consider that some passages of the readings may not be relevant to the learning content and thus, should be omitted. This implies that it is not acceptable to present a summary of each reading component sequentially, i.e., to

summarize each individual paper. Instead, relevant information should be synthesized across papers for presentation.

All students are expected to be prepared to discuss the content that was included in the readings and in their written assignments in class. Students are encouraged to bring supplemental information from additional readings or other materials that can enhance understanding of the topic. In past classes, students have shared a Dropbox folder to allow access to all materials they assembled, and we encourage that. You should be prepared to ask questions that spark discussion, promote critical thinking and even debate, and encourage the application of concepts to specific situations relevant to research in POP.

Weekly written assignments (should not exceed 1-2 pages): Faculty will post several discussion questions each week. Each student must submit his or her answers by noon of the day before class. Compliance with this deadline is critical to allow faculty time to read assignments. Answer each of the questions using cohesive paragraphs. Your paragraphs should be textual. Please do not use outlines or sentence fragments for your answers.

Class meetings: Students will be chosen to provide a synthesis of the reading materials related to the weekly topic. The synthesis should be organized according to the learning objectives that were posted for the week, cover the reading materials as well as additional material that the student has found to be useful to enhance discussion of the topic. Following this presentation, the selected student is then expected to lead the class in a discussion.
Each time a student's leads a discussion during class, performance will be graded on a scale of 0-5. Grading of performance in class meetings is based on the following criteria:

- Class presentation is well organized and provides an accurate and concise overview of the assigned topic
- The presentation uses examples or other additional material to emphasize or exemplify learning objectives
- Questions to the group reflect insightful understanding of the assigned readings
- Leader effectively encourages and leads discussion throughout the discussion period
- Leader summarizes key points raised during the discussion

Selection of a measurement instrument (group assignment, 2-3 students per group): During the course of the semester, you will be asked to conduct a review regarding measurement of commonly used outcomes. Because commonly used measures have a large volume of literature testing their reliability and validity, you will work in groups. You will summarize your findings in a presentation in class and a term paper that is due 1 week before the scheduled presentation.

The outcome that has been selected for this year is "effectiveness of medical marijuana as adjuvant therapy for chronic pain". Imagine that you are planning a study on the effect of new policy involving legalization of marijuana for medical use. One permitted indication per the new state law is chronic pain and in evaluating the risk benefit of the new policy, you have chosen to focus on benefit first. We are not interested in your study design, but rather your choice of a measure that is reliable, valid and stable across time. You are expected to present at least 3 different approaches in how the construct has been measured. For each approach present a published validation approach (if available) and discuss the strength and weaknesses of the approach. Then develop the "ideal" measure for your study.

GRADING

A	100%	to 94%
A-	< 94%	to 90%
B+	< 90%	to 87%
B	< 87%	to 84%
B-	< 84%	to 80%
C+	< 80%	to 77%
C	< 77%	to 74%
C-	< 74%	to 70%
D+	< 70%	to 67%
D	< 67%	to 64%
D-	< 64%	to 61%
F	< 61%	to 0%

ASSIGNMENTS

Measure selection/validation (group project)	25%
Final exam (in house, closed book)	25%
Leading class discussion	25%
Participation in class discussion	15%
Weekly assignments	10%

Criteria for grading of participation in class discussion:

15% - consistently active participation with independent contributions that enrich class content
12% - student is consistently well-prepared and participates in class discussion
10% - student is largely well-prepared but participates only when solicited
0% - student is consistently ill-prepared

Interim grades for participation in class discussion will be assigned three times throughout the course: after the end of week 4, week 8 and week 14.

Critical Dates

Group Presentation on Development and Validation of Clinical Measure	4/21
Final exam	4/28

Course outline

The table below provides an overview of all class sessions along with planned topics, learning objectives and readings. Note that some readings might change – make sure to check what is posted for each week on Canvas. Some class session dates may also change due to travel or department events. Assignments will be posted online in separate documents for each week.

Weeks shaded in grey are led by Dr. Goodin, unshaded weeks are led by Dr. Winterstein. **Please note that the listed readings may not be final. For each week, we will post a word document in Canvas that outlines the learning objectives, readings and assignments. Please refer to this document for all preparatory work. Materials will always be available one week before the actual meeting time.**

Date	Topic	Learning objectives	Readings
W1 1/7	Introduction to class		Kimberlin CL, Winterstein AG. Am J Health Syst Pharm. 2008; 65:2276-84
	Causal inference and scientific method	1. Describe key considerations in making causal inferences in science 2. Provide a brief overview of the evolution of theory of science and the scientific method	Rothman JK. Epidemiology: An Introduction. Oxford University Press. 2nd edition. Chapter 3: What is causation? Optional: Rothman KJ, Gallacher JEJ, Hatch EE. Why representativeness should be avoided. Int J Epidem 2013;42:1012-1014 - Commentaries and rebuttal following the article above: Int J Epidem 2013;42:1014-1028
	Constructs of health in clinical assessment	1. Explain the relationship of clinical outcomes to measurement constructs 2. Name some approaches to categorization of outcomes	Optinal: Starfield B. Measurement of Outcome – Proposed Scheme. The Milbank Quarterly, Vol. 83, No. 4, 2005 (pp. 1–11)
W2 1/14	Classical test theory	1. Define the process of measurement in science 2. Define key features of classical test theory	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Oxford University Press, Ontario, Canada. Chapter 1 & 2.
	Reliability	1. Define reliability per classical test theory 2. Explain the meaning of ICCs and the distinction between consistency versus absolute agreement	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Chapter 5 from "homogeneity of items". Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Chapter 8 until section "different forms of the reliability coefficient".
	Interpretation of reliability coefficients	1. Compare and contrast the meaning, advantages, and disadvantages of various reliability coefficients 2. Describe the relationship between reliability coefficients and sample size	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Oxford University Press, Ontario, Canada. Chapter 8 from "different forms of the reliability coefficient" until "reliability generalization". Krell RW, Hozain A, Kao LS, Dimick JB. Reliability of Risk-Adjusted Outcomes for Profiling Hospital Surgical Quality. *JAMA Surg.* 2014;149(5):467–474. doi:10.1001/jamasurg.2013.4249
	Measure generalizability	1. Describe key considerations in generalizing measure reliability	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Chapter 8 from "reliability generalization". Boonstra AM, et al. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. International Journal of Rehabilitation Research 2008;31(2):165-169.
W3 1/21	Validity	1. Define validity in the context of classical test theory and theory of science 2. Explain the use of content, criterion, construct, discriminant and convergent validation approaches to assess validity 3. Explain the concept of responsiveness and sensitivity to change in measure validation	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Chapter 10. Validity. Read up to "Validity and types of indices". McHorney CA et al. The MOS-36-Item Short-Form Health Survey: II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care* 1993; 31:247-263.
	Item Response Theory (IRT)	1. Describe the strengths and weaknesses of IRT compared to Classic Test Theory (CTT)	Hays RD, Morales LS, Reise SP. Item Response Theory and Health Outcomes Measurement in the 21st Century. Medical care. 2000;38(9 Suppl):II28-II42.

		2. List key considerations for choosing IRT over CTT	Embretson SE: The new rules of measurement. Psychological Assessment 8: 341–349, 1996. DeWalt DA, et al. Evaluation of Item Candidates: The PROMIS Qualitative Item Review. *Medical Care* 2007;45(S1): S12-S21.
	Criterion validation	1. Define validation approaches for clinical measures of disease 2. Define and rank the relevance of sensitivity, specificity and positive predictive value for different clinical and research scenarios 3. Explain ROC curves	Wiley LK, et al. ICD-9 tobacco use codes are effective identifiers of smoking status. Journal of the American Medical Informatics Association: JAMIA. 2013;20(4):652-658. doi:10.1136/amiajnl-2012-001557. Chen G et al. Validating ICD9 coding algorithms for diabetes mellitus from administrative data. Diab Res Clin Pract 2010;89:189-195. Martin, Greg, et al. "The Severity of Dependence Scale (SDS) in an adolescent population of cannabis users: reliability, validity and diagnostic cut-off." Drug and Alcohol Dependence83.1 (2006): 90-93.
W4 1/28	Patient-reported outcomes	1. Define the construct of patient-reported outcomes and discuss their relevance in the assessment of drugs and healthcare service 2. Describe how patient-reported outcomes measurement is implemented	McKenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. BMC Medicine 2011; 9(1), 86.
	PRO item selection	1. Describe ways to identify items for PROs 2. Define key features of content validity of a PRO and how it is assessed 3. List key considerations for item selection in PRO development	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Chapter 3 and 5 until section “homogeneity of the items” Rothman M, Burke L, Erickson P et al. Use of existing patient-reported outcome (PRO) instruments and their modification: Value in Health 2009; 12(8): 1075-83.
	PRO response scales	1. Compare advantages of continuous versus categorical PRO response scales 2. Describe examples of direct PRO estimation methods and discuss advantages and disadvantages 3. Name examples of comparative PRO scaling methods	Streiner DL, Norman GR, Cairney J. Health measurement scales. 5th edition. 2015. Oxford University Press, Ontario, Canada. Chapter 4 “Scaling responses” and Chapter 6 “Biases in responding”
	PRO in HSR and PharmEpi	1. Explain how and why PRO is used for different purposes in HSR and PharmEpi	Elliot MN, et al. *Patterns of Unit and* Item Nonresponse in the CAHPS Hospital Survey. Health Services Research 2005;40(6): 2096-2119. England LJ, et al. Misclassification of maternal smoking status and its effects on an epidemiologic study of pregnancy outcomes. Nicotine & Tobacco Research 2007;9(10), 1005-1013.
W5 2/4	Measuring mortality	1. Describe the coding conventions for cause of death 2. Identify limitations of cause of death data	Introduction into measurement of death: http://www.deathreference.com/Bl-Ce/Causes-of-Death.html Anderson RN et al. Comparability of Cause of Death between ICD–9 and ICD–10: Preliminary Estimates. NVSS 2001;49(2)
	Patient/Consumer-Generated Data	1. Identify potential sources of novel patient-generated data 2. Describe uses of patient, consumer, or tech-generated data for assessment of health outcomes 3. Identify strengths and limitations of patient-generated data	Incorporating Patient Generated Health Data into Pharmacoepidemiological Research. Available at course website.

			Wood WA, Bennett AV, Basch E. Emerging uses of patient generated health data in clinical research. Molecular oncology. 2015 May 1;9(5):1018-24. Charles-Smith LE, Reynolds TL, Cameron MA, Conway M, Lau EH, Olsen JM, Pavlin JA, Shigematsu M, Streichert LC, Suda KJ, Corley CD. Using social media for actionable disease surveillance and outbreak management: a systematic literature review. PloS one. 2015 Oct 5;10(10):e0139701.
	Surrogate endpoints	1. Describe key requirements for a surrogate endpoint to serve as valid proxy for the measurement of a drug effect 2. Describe key challenges in establishing epidemiologic evidence for the link between a surrogate and hard clinical endpoint.	Fleming TR. Surrogate endpoints and FDA/s accelerated approval process. Health Affairs 2005;24:67-78. Riddle MC et al. Epidemiologic relationship between A1c and all-cause mortality during a median 3.4-year follow-up glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983-90
W6 2/11	EHR & claims data	1. Summarize key issues with the use of EHR data in drug safety and effectiveness research. 2. List approaches to evaluate the quality of EHR data 3. Compare and contrast the validity of outcomes definitions using EHR versus claims data	Caveats for the Use of Operational Electronic Health Record Data in Comparative Effectiveness Research. Medical Care. 2013;51: S30-S37 Data Quality Assessment for Comparative Effectiveness Research in Distributed Data Networks. Medical Care. 2013;51: S22-S29 Terris et al. Health State Information Derived from Secondary Databases was affected by Multiple Sources of Bias. J Clin Epidemiol. 2007 July; 60(7): 734–741.
W7 2/18	Misclassification of outcomes	1. Describe common ways how outcomes can be misclassified by inappropriate or invalid data ascertainment methods 2. Explain the concepts of differential and non-differential misclassification 3. Describe how misclassification of outcomes affects the estimate of associations between exposure and outcomes	Hartzema AG and Schneeweiss S. Addressing misclassification in pharmacoepidemiologic studies. (Chapter 13) in: Hartzema et al (ed) Pharmacoepidemiology and Therapeutic Risk Management, Harvey Whitney Books, Cincinnati, OH 2008 Setoguchi S et al. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between Medicare claims and cancer registry data. Cancer Causes Control 2007;18:561-569
	Composite endpoints	1. Describe the advantages and disadvantages in utilizing composite endpoints 2. List the key requirements for the composition of multiple endpoints in safety or efficacy assessments	Montori VM et al. Validity of composite end points in clinical trials. BMJ 2005;330:594-f Ignacio Ferreira-González et al. Problems with use of composite end points in randomised controlled trials cardiovascular trials: systematic review of trials BMJ 2007;334;786 Tomlinson et al. Composite End Points in Randomized Trials: There Is No Free Lunch. JAMA.2010; 303: 267-268
	Addressing outcomes misclassification	1. Describe approaches to address outcomes misclassification	Funk MJ et al. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. Curr Epidemiol Rep 2014;1:175-195 Magder LS, Hughes JP. Logistic regression when the outcome is measured with uncertainty. Am J Epi 1997;146:195-203
W8 2/25	Drug exposure measurement	1. Explain how dose and duration can be summarized to quantify exposure and discuss strengths and weaknesses of various approaches	Wettermark B et al. Drug Utilization Research. In: Hartzema et al (ed) Pharmacoepidemiology and Therapeutic Risk Management, Harvey Whitney Books, Cincinnati, OH 2008, pages 159-174 Raebel et al. Standardizing Terminology and Definitions of Medication Adherence

			and Persistence in Research Employing Electronic Databases. Medical Care 2013;51:S11-21 Van Staa TP et al. oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology 2000;39:1383-1389
	Exposure mis-classification	1. Describe common sources of exposure misclassification in drug studies 2. Estimate the impact of exposure misclassification on association estimates 3. Describe approaches to address exposure misclassification in studies on drug effects	Hartzema AG and Schneeweiss S. Addressing misclassification in pharmacoepidemiologic studies. (Chapter 13) in: Hartzema et al (ed) Pharmacoepidemiology and Therapeutic Risk Management, Harvey Whitney Books, Cincinnati, OH 2008. Funk MJ et al. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. Curr Epidemiol Rep 2014;1:175-195 Bodnar et al. The Impact of Exposure Misclassification on Associations Between Prepregnancy BMI and Adverse Pregnancy Outcomes. Obesity 2010
W9 3/10	Time in measuring risk	1. Describe different ways and provide examples how associations between drugs and outcome can vary over time 2. Describe the set-up of time-varying exposure and how drug exposure windows can be varied to determine the duration and intensity of drug effects, including depletion of susceptibles 3. Describe how measures of exposure duration or intensity can be incorporated into the time-varying exposure definitions.	Rothman KJ and Greenland S. Cohort Studies. In: Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd Edition. 2008, Philadelphia, PA Stricker BHCh and Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol 2010;24:245-251 Suissa S et al. First-time use of newer oral contraceptives and the risk of venous thromboembolism. Contraception 1997;56:141-146 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-920 Drug exposure risk windows and unexposed comparator groups for cohort studies in Pharmacoepidemiology. PDS 1998;7:275-280
	Time-related biases	1. Describe time-related biases including time window bias and immeasurable time bias. 2. Describe approaches in design and analysis that address time-varying effects 3. Describe immortal time bias and discuss design and analytical solutions.	Suissa S et al. Time-window bias in case control studies: statins and lung cancer. Epidemiology 2011;22:228-231 Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. Am J Epidemiol 2008;168:329-35 Suissa S. Immortal time bias in observational studies of drug effects. PDS 2007;16(3):241-249 Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167 (4): 492-499. Suissa S et al. Metformin and the risk of cancer. Diabetes Care 2012;35:2665-2673 Zhou Z et al. Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods. Am J Epidemiol 2005;162 (10): 1016-1023
W10 3/17	DAGs	1. Describe principles of causal diagrams 2. Explain confounding using DAGs	Modern Epidemiology page 87-127 Greenland S et al. Causal diagrams for epidemiologic research. Epidemiology 1999;10(1):37-48

	Selecting and measuring confounders	1. Delineate a strategy to establish a comprehensive set of confounders that should be considered for adjustment in causal inference studies. 2. Discuss strategies to select confounders for inclusion in multivariate adjustment.	Klein-Geltink JE et al. Readers should systematically assess methods used to identify, measure and analyze confounding in observational cohort studies. JCE 2007;60(8):766.e1-11 Sauer BC et al. A Review of Covariate Selection for Nonexperimental Comparative Effectiveness Research. Pharmacoepidemiol Drug Saf. 2013 Nov;22(11):1139-45. Schisterman EF et al. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology. 2009 Jul; 20(4): 488–495.
W11 3/24	Identify types of missingness	1. Describe types of missingness in epidemiological research 2. Discuss approaches to identify different types of missingness.	Neil J. Perkins, Stephen R. Cole, Ofer Harel, Eric J. Tchetgen Tchetgen, BaoLuo Sun, Emily M. Mitchell, and Enrique F. Schisterman Principled Approaches to Missing Data in Epidemiologic Studies. Am J Epidemiol 2017; 187 (3) Janssen et al. Missing covariate data in medical research: To impute is better than to ignore. J Clin Epidem. 2010;63:721-727
	Measurement in prediction (taught by Dr. Shao)	1. Describe validation approaches of prediction models 2. Describe key concepts to measure the validity of prediction models 3. Apply best practices of prediction model validation in evaluating published studies on risk score development	Steyerberg EW. Validation of prediction models. In Steyerberg EW. Clinical prediction models. Springer, NY, 2009 Steyerberg EW, Vickers AJ, Cook NR et al. Assessing the performance of prediction models. Epidemiology 2010;21:128-138
W12 3/31	Misclassified confounders	1. Describe types and examples of confounder misclassification 2. Describe the parameters that define the direction and strength of impact of misclassified or unmeasured confounders on associations 3. Describe how the impact of residual confounding can be estimated	Hartzema AG and Schneeweiss S. Addressing misclassification in pharmacoepidemiologic studies. (Chapter 13) in: Hartzema et al (ed) Pharmacoepidemiology and Therapeutic Risk Management, Harvey Whitney Books, Cincinnati, OH 2008 Oliveira et al. self-reporting weight and height: misclassification effect on the risk estimates for acute myocardial infarction. Europ J Publ Health 2009 Knol et al. Unpredictable bias when using the missing indicator method or complete case analysis for missing confounder values: an empirical example. J Clin Epi 2010;63:728-736 Gamble et al. Quantifying the Impact of Drug Exposure Misclassification due to Restrictive Drug Coverage in Administrative Databases: A Simulation Cohort Study. Available at: http://www.sciencedirect.com/science/article/pii/S1098301511015671 Funk MJ et al. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. Curr Epidemiol Rep 2014;1:175-195
W13 4/7	Addressing misclassified confounders	1. Describe ways to address residual confounding with external information 2. Describe the general application of instrumental variables to address residual confounding	Schneeweiss S et al. Adjusting for Unmeasured Confounders in Pharmacoepidemiologic Claims Data Using External Information. Epidemiology 2005;16: 17–24 Brookhart et al. Evaluating Short-Term Drug Effects Using a Physician-Specific Prescribing Preference as an Instrumental Variable. Epidemiology 2006;17: 268–275
W14 4/14	Measurement synthesis	1. Discuss case studies of “failed” measurement	“The Basement Tapes”. This podcast episode traces the story of a landmark clinical trial conducted in the 1960s, upon which most US guidelines for nutrition advice were based. When re-analyzed by contemporary epidemiologists rampant measurement error was identified that, when adjusted for, reversed the study

			findings. Other case TBD
	Prelim Preparation	1. Examine examples of past prelim exam questions and responses 2. Complete a prelim practice exam	Read the prelim example questions and responses document posted on the course website.
4/21	Presentation of group assignments (Note that they date will need to be changed due to ISPE Midyear)		
4/28	Exam		

Class Attendance Policy
Requests for excused absences MUST be made by email to the course coordinator prior to the scheduled session.

Other relevant policies:
The College of Pharmacy has a website that lists course policies that are common to all courses. This website covers the following:

1. Class Attendance, Make-up Exams and Other Work
2. University Grading Policies for Assigning Grade Points
3. Concerns, Appeals, and Complaints
4. Academic Integrity Policy
5. How to request learning accommodations
6. Faculty and course evaluations
7. Computer and Other Technology Requirements
8. Student expectations in class
9. Discussion board policy
10. Email communications
11. Religious holidays
12. How to Contact Counseling & student health Services
13. How to access services for student success
14. Faculty Lectures/Presentations Download Policy

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