# About This Course

Welcome:

When I was a student in DOC Research it helped me to design and to conduct my own clinical and outcomes research, and I hope to return that favor to each of you. This course can be taken as a stand-alone class for clinicians who want help designing and conducting their own research or as a requirement for a master’s of science in clinical investigation (MSCI) or other graduate degree at Washington University in St. Louis.

Teaching Philosophy:

At the beginning of each class, the course TA and I will provide you with a paper copy of the PowerPoint slides that the lecturer will use that day (except for last-minute changes). We also will post an electronic copy of the slides on [blackboard](https://bb.wustl.edu/). If you don’t understand something the lecturer says, please ask your question during the lecture; you don’t have to save questions until the end of class. Although we recommend that you do the readings before class, we understand that sometimes reading gets deferred until after class.

A good way to reinforce the course material is to use your favorite journal as a collection of case studies: After you read the title and background of a study, set the journal down and ask yourself how you would conduct the study. What study design would you have used? Whom would you have enrolled? What methods would you have used to enhance casual inference? How would you analyze the data? This reflection will make you a better researcher and help you remember the study.

Required Texts**:**

Required Text: Designing Clinical Research (4th ed). Stephen Hulley et al. Lippincott Williams & Wilkins (2013). ISBN-13: 978-1608318049. This book is available as an e-book via Bernard-Becker Library.

Course Materials**:**

Printouts available at each class; electronic copy on <https://bb.wustl.edu>.

Course Location**:**

The course is taught in the General Medical Sciences (GMS) conference room, which is in the Taylor Avenue Bldg. (labeled, "Institute of Public Health"). After entering the building by the flagpole, walk past the abandoned Well Aware gym, through the unmarked door, and zig-zag down the long yellow-green hallways until you see the entrance to GMS. Instead of entering look over your right shoulder and you’ll see the GMS classroom. However, on Wednesday, Sept 12, the class will be taught on the 2nd floor of the Taylor Avenue Bldg.

Course Description**:**

DOC Research covers how to select a clinical research question, outline a research protocol, and execute a clinical study. Topics include: volunteer selection, observational and experimental study designs, sample size estimation, clinical measurement, bias and confounding, and data management. The course is designed for health care professionals who wish to conduct patient-oriented clinical research. Students incorporate research design concepts into their own research proposal. The course consists of lectures, weekly problem sets, weekly reading assignments, a 2-page protocol, and a final exam.

**Target audience:**

Students who already have or are pursuing any of the following degrees: MSCI, MPH, MSPH, ANP, MD, DO, DPT, OTD, Pharm D, or a PhD in nursing, rehabilitation/participation science, or medical anthropology. Although there is no formal prerequisite, some clinical background is assumed as we will discuss how to design studies of common diseases, such as: hypertension, carpal tunnel syndrome, neural tube defects, and pulmonary embolism.

Goals of the Course**:**

By the end of this course, participants will be able to:

* Design an outcomes, clinical, or translational research study
* Execute the research study
* Evaluate the strengths and weakness of alternate study designs
* Read the medical literature critically.

# **Time Requirements**

The time commitment for this course is ~9 hours a week.

# About the Coursemaster Brian F. Gage, MD, MSc is a physician–scientist whose research focuses on antithrombotic therapy and thrombosis. He is a Professor of Medicine at Washington University. He sees patients at Barnes-Jewish Hospital, where he directs the Clinical-Scientist Teaching And Research [(C-STAR)](http://ghs.wustl.edu/cstar.html) program for medical residents. He also directs the Washington University Fellowship in General Medical Sciences [(GMS Fellowship)](https://generalmedicalsciences.wustl.edu/education/fellowship/) and serves as co-director of the Biostatistics, Epidemiology, and Research Design ([BERD](http://icts.wustl.edu/icts-researchers/icts-cores/find-services/by-core-name/research-design-biostatistics-group)) core of the CTSA.

Dr. Gage has a BS (biology) and MSc (health services research) from Stanford University and an MD from the University of California, San Diego. He completed his internship and chief residency at the Good Samaritan/Phoenix VA Medical Center, his internal medicine residency at Barnes-Jewish Hospital, and his fellowship (in general internal medicine) at the Palo Alto VA/Stanford University.

From 2010 – 2017, Dr. Gage was the principal investigator of the Genetic InFormatics Trial (GIFT) of Warfarin Therapy to Prevent DVT Trial.  To make the GIFT warfarin dosing algorithms publicly available, he operates a non-profit website, [(www.WarfarinDosing.org)](http://www.warfarindosing.org/Source/Home.aspx). Previously, he developed clinical prediction rules to predict stroke [(CHADS2)](http://jamanetwork.com/journals/jama/fullarticle/193912) and hemorrhage [(HEMORR2HAGES)](http://www.warfarindosing.org/Source/PredictionRule.aspx).

Contact Information**:**

Name: Brian F. Gage, MD, MSc.

Phone number: 314 454-8697

Email address: [bgage@wustl.edu](mailto:bgage@wustl.edu)

Campus office: GMS, Suite 155 in the Taylor Avenue Building (TAB)

Preferred method of contact: email

In-Person Office Hours: Mondays, 9:10-10:45 AM in Dr. Gage’s office except for Sept 10. To make an appointment at a different time, please email.

**Teaching Assistant (TA):**

Name: Julianne Sefko, MPH

Phone number: 314 747-2496

Email address: [jsefko@wustl.edu](mailto:jsefko@wustl.edu)

Preferred method of contact: email

**Course Schedule** (may be revised)

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| Dates | Topic | Readings | Hulley Chapters\* | Assignments Due |
| Aug 29 | 4:00 Refining the research question & FINER research: Dr. Gage | Revising a Research Protocol (handout)  Kahn, CR. *Picking a Research Problem: The Critical Decision*[N Engl J Med](http://www.nejm.org/doi/full/10.1056/NEJM199405263302113)1994.  P. Ridker et al. **Abstract** to: *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease* [New Engl J Med](http://www.nejm.org/doi/full/10.1056/NEJMoa1707914) 2017. | 1, 2 | *Get Problem Set 1 and Syllabus* |
| 5:05 Couse overview; protocol outline Dr. Gage | Outline of a Study Protocol (handout)  ASCEND investigators [New Engl J Med](https://www.nejm.org/doi/full/10.1056/NEJMoa1804988) 2018. |  |
| Sept 5 | 4:00 Reproducibility in research; type I & II errors; Ho & HA; p-values | (Optional: Haynes RB. Forming Research Questions.)  (Optional: Install Excel data analysis pac: Excel button> Excel options > Add-ins > Analysis Toolpack > Go) | 5, 6 | **Due Problem Set 1;** *Get Problem Set 2* |
| 4:40 Normal distribution, α, β, Power, and continuous data; t-test. | (Optional: Bigby M, Gadenne AS. Understanding and evaluating clinical trials.  [J Am Acad Dermatol. 1996;34:563-77](http://www.ncbi.nlm.nih.gov/pubmed/8601646).; if interested, you can read the whole article.) |  |
| 6:00 Preview: observational study designs |  |  |
| Sept 12 | 4:00 Cohort studies: incidence rates, RR, confounding | (Carlsson L. et al. Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects [N Engl J Med 2012.](http://www.nejm.org/doi/full/10.1056/NEJMoa1112082)  Ray et al. Dual-cohort study of Azithromycin [N Engl J Med 2012](http://www.ncbi.nlm.nih.gov/pubmed/22591294)) | 3 & 4 appendix 12A | **Due Problem Set 2;** *Get Problem Set 3* |
| 4:50 Chi-square, Power Analyses of binary data |  |  |
| 5:25 Cross-sectional & case-control studies: OR | Lagergren J. et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma [N Engl J Med 1999](http://www.nejm.org/doi/full/10.1056/NEJM199903183401101). | 7, 8 |
| Sept 19 | 4:00 Nested case-control studies & Case cross-over studies |  | p. 171-179 | **Due Problem Set 3;** *Get Problem Set 4* |
| 5:05 Randomized Trials: **Dr. Kollef** |  | 10 |
| Sept 26 | 4:00 Accuracy, precision, &  Agreement: **Dr. Yusen** |  | 4 | **Due: Problem Set 4;** *Get Problem Set 5* |
| 5:10 Diagnostic testing: sensitivity, specificity, predictive value and ROC curves |  | p. 180-189 |
| Oct 3 | 4:00 Other Study Designs:  Cross-over trials;  Method of Zelen; Composite outcomes; & Non-inferiority trials | [(Optional: Short Blessed screening for dementia)](http://mybraintest.org/dl/ShortBlessedTest_WashingtonUniversityVersion.pdf)  Freemantle N et al. Composite outcomes in randomized trials: greater precision but with greater uncertainty? [JAMA 2003](http://www.ncbi.nlm.nih.gov/pubmed/12759327)  Mauri & d’Agostino. Challenges in the Design and Interpretation of Noninferiority Trials [New Engl J Med](https://www.nejm.org/doi/pdf/10.1056/NEJMra1510063) 2017.  (Optional**:** A-M Chang et al. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. [PNAS 2014](http://www.pnas.org/content/early/2014/12/18/1418490112).)  Prather et al. Behaviorally Assessed Sleep and Susceptibility to the Common Cold [Sleep 2015](http://www.journalsleep.org/ViewAbstract.aspx?pid=30153) | 11 | **Due: Problem Set 5;** *Get Problem Set 6*  Due: 5 copies of your protocol outline (3 pages if 1.5-spaced, excluding references) |
| 5:10 Review of protocols |  |  |
| Oct 10 | 4:00 Ethics | Belmont Report (part B), Declaration of Helsinki,  (Optional Shalowitz,D Miller, F. Disclosing Individual Results of Clinical Research JAMA 2005;294:737-740) | 14 | **Due: Problem Set 6;** *Get Problem Set 7* |
| 5:10 Clinical Prediction Rules | C. Lindsey et al. Prognostic Indices for Older Adults: A Systematic Review [JAMA 2012;307,182-192.](http://jama.jamanetwork.com/article.aspx?articleid=1104837) | pp. 180-182 |
| Oct 17 | 4:00 Enhancing Causal Inference: **Dr. Evanoff** | Selby JV. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer [N Engl J Med 1992.](http://www.ncbi.nlm.nih.gov/pubmed/1736103)  Rothman and Greeenland. Causation and Causal Inference in Epidemiology [Am J Public Health](https://www.ncbi.nlm.nih.gov/pubmed/16030331) 2005.  (Optional: Abstract to: Wacholder S. et al. Performance of Common Genetic Variants in Breast-Cancer Risk Models **N Engl J Med** 2010.)  (Optional: order Gallin et al. Principles and Practice of Clinical Research 4th ed) | 9 | **Due: Problem Set 7;** *Get Problem Set 8* |
| 5:10 Linear regression | Katz MH. Multivariable Analysis: A Primer for Readers of Medical Research [Ann Intern Med](http://www.ncbi.nlm.nih.gov/pubmed/12693887) 2003. |  |
| Oct 24 | 4:00 Outcomes Research: **Dr. Piccirillo** |  |  | **Due: Problem Set 8;** *Get Problem Set 9* |
| 5:10 Logistic regression |  |  |
| Oct 31 | 4:00 Propensity Score | J Haukoos and R Lewis. The Propensity Score [JAMA](http://jama.jamanetwork.com/article.aspx?articleid=2463242) 2015 | pp 128-132,  Chapter 13 | **Due: Problem Set 9:** Email your protocol outline by 11:59 p.m. on Nov 5 |
| 5:10 Cox proportional hazards regression | Gallin et al. Principles and Practice of Clinical Research 4th ed chapter 26.  For your protocol outline, your subject line should use this format: “DOC Research Protocol Outline: Smith”, where “Smith” is your last name |  |
| Nov 7 | 4:00 Meta-analysis: Dr. Gage | M. Murad et al. How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care Users’ Guides to the Medical Literature [JAMA](http://jama.jamanetwork.com/article.aspx?articleid=1886196) 2014.  (Optional Selective publication of antidepressant trials and its influence on apparent efficacy [N Engl J Med 2008](http://www.ncbi.nlm.nih.gov/pubmed?term=18199864)) | 13 | **Due: Problem Set 10** Get Problem Set 11 |
| 5:10 Cost-effectiveness analyses: Dr. Gillespie | (Optional: Shah & Gage. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. [Circulation 2011;123](http://www.ncbi.nlm.nih.gov/pubmed/21606397)) | 16 |
| Nov 14 | 4:00 Managing the Research Team: **Dr. Dale** |  | 9, 19 | **Due: Problem Set 11;** *Get problem Set 12 and practice final* |
| 5:00 Data management, biorepositories, Study implementation & Quality | [http://www.biostat.wustl.edu/redcap/wusm\_REDCap.html, NIH policy on data sharing, PubMed Central and NIH Public Access policy](http://www.biostat.wustl.edu/redcap/wusm_REDCap.html,%20%20NIH%20policy%20on%20data%20sharing,%20PubMed%20Central%20and%20NIH%20Public%20Access%20policy) | 17 |
| Nov 21 | Class cancelled: Happy Thanksgiving | | | |
| Nov 28 | 4:00 QI & Patient Safety: **Dr. Fondahn** | (Optional: Guyatt GH. and Haynes RB. Preparing reports for publication and responding to reviewers' comments) | 16 | **Due: Problem Set 12** |
| 5:10 Final exam review | Practice final |  |
| Nov 30 | 3:00-5:00 Final Exam offering #1 | Optional final date |  |  |
| Dec 5 | Public health; Effect modifications; & Scientific figures & | Equity impacts of price policies to promote healthy behaviours [Lancet](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30531-2/fulltext) 2018  (Optional: Pietrobon. Manuscript Architect : A web-based application for scientific writing **BMC Medical Informatics and Decision Making** 2005 5:15.) | 17 | **Due: nil** |
| 5:10 Case studies of pitfalls in clinical research: budgets, personnel challenges, recruitment woes, audits. | TBD |  |
| Dec 10 | Extended office hours | 9:00-noon |  |  |
| Dec 12 | 4:00 Final Exam | You will *not* need a calculator nor your notes. |  |  |

**\*** Reading should be done prior to lectures (except lecture 1). Readings in parentheses are optional.

# Assessment/Grading

Grade Composition**:**

The final is ~39% of the course grade, the protocol outline ~8%, the problem sets ~53%. If a student’s average falls between two grades in the table below, in-class participation will be used to determine whether the grade should be rounded up or down.

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| --- |
| **Grade (Percent of Points)** |
| A+ (98.5% to 100%)  A (93.0% to 98.4%)  A- (90.0% to 92.9%) |
| B+ (88.5% to 89.9%)  B (83.0% to 88.4%)\*  B- (80.0% to 82.9%) |
| C+ (78.5% to 79.9%)  C (73.0% to 78.4%)  C- (70.0% to 72.9%) |

**\*** Minimum for core courses if getting an MSCI

**Late Assignments:**

Assignments are due at the beginning of class. For each day (calculated at 12:01 AM) that an assignment (except for assignment 1) is late the score is multiplied by 0.93. For example, a perfect assignment submitted 3 days late would score 80.4%. To avoid a late penalty if you will be away when an assignment is due, email it to [Julianne Sefko, MPH](mailto:jsefko@wustl.edu) with this subject line: **DOC Research Problem Set *N***, (where ***N*** is the problem set #).

Attendance Requirement:

In-class participation is an important part of the course. Students are expected to physically attend at least 75% of class sessions; if you anticipate missing > 25% of class sessions you should not sign up for this course. Watching the videotaped class presentations is helpful to keep up with missed sessions, but does not count as class attendance. Students whose professional duties or personal circumstances unexpectedly prevent them from meeting the attendance requirement will have the opportunity to make up 1 missed class.

**Technology Usage During Class:**

When class starts, please turn down the volume of ringers and pagers. If you plan to use your laptop during class, don’t sit in the front row.

Feedback and Grading Timeline:

Problem sets will be returned 1 week after they are submitted. Protocol outlines will be returned 2-3 weeks after they are submitted.

# Technical Support

If you have any technical problems accessing [Blackboard](https://bb.wustl.edu/webapps/login/) please e-mail [crtc@email.wustl.edu](mailto:crtc@email.wustl.edu). Note that this mailbox is not monitored in the evening or on weekends. If you need immediate help after hours please put a service request into <https://wusm.service-now.com>.

# Course Policies

## Participation (Expectations):

Our classroom environment should promote the respectful exchange of ideas.

* Successful completion of this course requires that a student keep up with assignments and participate in all course activities.

**Drop Dates:**

You can drop for any reason during the course of the semester. However, you may only receive a partial or no tuition reimbursement depending upon how far into the semester you drop the course. See the [Academic Calendar](https://crtc.wustl.edu/courses/class-list/registration/academic-policies/) for your program for specific dates and reimbursement policies. Late withdrawals will appear on your transcript as a withdrawal.

CRTC Academic Policy Guidelines:

Guidelines regarding CRTC course registration and enrollment, grades, tuition obligation, and academic leave are consolidated in the [CRTC Academic Policy Guidelines](https://crtc.wustl.edu/wp-content/uploads/2016/04/AcademicRegulations_Current.pdf).

CRTC Guidelines for Academic and Non-Academic Transgressions:

By registering for this course you have agreed to the terms of the [CRTC Guidelines for Academic and Non-Academic Transgressions](http://crtc.wustl.edu/files/AcademicNon-AcademicTransgressionsGuidelines.pdf).

## Academic Integrity/Plagiarism:

* Academic dishonesty is a serious offense that may lead to probation, suspension, or dismissal from the University. One form of academic dishonesty is plagiarism – the use of an author's ideas, statements, or approaches without crediting the source. Academic dishonesty also includes copying information from another student.
* Academic dishonesty will be reported to the Office of the Registrar for possible action. The coursemaster will make an academic judgment about the student’s grade. The CRTC process regarding academic dishonesty is described in the [CRTC Guidelines for Academic and Non-Academic Transgressions](https://crtc.wustl.edu/wp-content/uploads/2016/04/AcademicRegulations_Current.pdf)

**Writing Assistance:**

For additional help on your writing, consult the expert staff of [The Writing Center](http://writingcenter.wustl.edu/) in Olin Library (first floor). It can be helpful to ask someone to read your prose and to provide feedback on strength of argument, clarity, organization, etc.

**Disability Resources:**

Washington University is committed to providing accommodations and/or services to students with documented disabilities. Washington University’s [Cornerstone:  Center for Advanced Learning Disability Resources](http://cornerstone.wustl.edu/disability-resources) is the University’s official resource for students with disabilities and students with suspected disabilities. They assist students with disabilities by providing guidance and accommodations to ensure equal access to our campus, both physically and academically. To learn more about its services, initiate the process of formal documentation and/or to arrange for accommodations, please contact [Disability Resources](http://cornerstone.wustl.edu/disability-resources) at the start of the course.

**Mental Health Resources:**

Mental Health Services’ professional staff members work with students to resolve personal and interpersonal difficulties that may affect the academic experience. These include conflicts with or worry about friends or family, concerns about eating or drinking patterns, and feelings of anxiety and depression. See: <http://shs.wustl.edu/MentalHealth>.

**Reporting Policies:**

Please also [review the CRTC website for policies](https://crtc.wustl.edu/courses/class-list/registration/academic-policies/reporting-policies/) regarding sexual assault reporting and reporting concerns about bias, prejudice or discrimination.

# CTSA Core Competencies for Master’s Degree Candidates

The following Clinical and Translational Science Award (CTSA) competencies are met by this course.

|  |  |
| --- | --- |
| **Core Thematic Areas** | **Competencies** |
| **I. CLINICAL AND TRANSLATIONAL RESEARCH QUESTIONS** | * Identify clinical studies they have testable research hypotheses. * Identify research observations that could be the bases of clinical trials. * Define the data that formulate research hypotheses. * Derive translational questions from clinical research data. * Prepare the background and significance sections of a research proposal. |
| **II. LITERATURE CRITIQUE** | * Identify potential sources of bias and variations in published studies. * Interpret published literature in a causal framework. * Identify gaps in knowledge within a research problem. |
| **III. STUDY DESIGN** | * Formulate a well-defined clinical or translational research question to be studied in human or animal models. * Propose study designs for addressing a clinical or translational research question. * Assess the strengths and weaknesses of possible study designs for a given clinical or translational research question. * Design a research study protocol. * Identify a target population for a clinical or translational research project. * Identify measures to be applied to a clinical or translational research project. * Design a research data analysis plan. * Determine resources needed to implement a clinical or translational research plan. * Prepare an application to an IRB. |
| **IV. RESEARCH IMPLEMENTATION** | * Compare the feasibility, efficiency, and ability to derive unbiased inferences from different clinical and translational research study designs. * Assess threats to internal validity in any planned or completed clinical or translational study, including selection bias, misclassification, and confounding. * Integrate elements of translational research into given study designs that could provide the bases for future research. |
| **V. SOURCES OF ERROR** | * Describe the concepts and implications of reliability and validity of study measurements. * Evaluate the reliability and validity of measures. * Assess threats to study validity (bias) including problems with sampling, recruitment, randomization, and comparability of study groups. * Differentiate between the analytic problems that can be addressed with standard methods and those requiring input from biostatisticians and other scientific experts. * Implement quality assurance systems with control procedures for data intake, management, and monitoring for different study designs. * Assess data sources and data quality to answer specific clinical or translational research questions. * Implement quality assurance and control procedures for different study designs and analysis. |
| **VI. STATISTICAL APPROACHES** | * Describe the basic principles and practical importance of random variation, systematic error, sampling error, measurement error, hypothesis testing, type I and type II errors, and confidence limits. * Scrutinize the assumptions behind different statistical methods and their corresponding limitations. * Compute sample size, power, and precision for comparisons of two independent samples with respect to continuous and binary outcomes. * Describe the uses of meta-analytic methods. |
| **VII. BIOMEDICAL INFORMATICS** | * Access patient information using quality checks via electronic health record systems. |
| **VIII. RESPONSIBLE CONDUCT OF RESEARCH** | * Summarize the history of research abuses and the rationale for creating codes, regulations, and systems for protecting participants in clinical research that requires community input. * Explain the special issues that arise in research with vulnerable participants and the need for additional safeguards. * Describe the elements of voluntary informed consent, including increasing knowledge about research, avoiding undue influence or coercion, and assuring the decision-making capacity of participants. |
| **XI. TRANSLATIONAL TEAMWORK** | * Build a multidisciplinary team that matches the objectives of the research. * Manage a clinical and/or translational research study. |