Instructors:  
Merrick Zwarenstein: merrick.zwarenstein@ices.on.ca  
Neil Klar: nklar@uwo.ca

Office Hours: Email for appointment

The 9566S graduate course (same content as first half of 4715B undergraduate course) is a prerequisite for and complement to the 9586T graduate course (same content as second half of 4715B undergraduate course).

First half: 6 weeks-January 11 – February 15; venue: PHFM 3015
In person class: Merrick Zwarenstein: Wednesdays; 1.30-2.45 and 3.15-4.30 p.m.

Second half: 6 weeks- March 1 – April 5; venue: PHFM 3015
In person class: Merrick Zwarenstein: Wednesdays; 1.30-2.45
Neil Klar: Wednesdays; 3.00-4.30 p.m.

Reading week: February 18-26 (no classes).

Course Information
Graduate Pre-requisites: Biostatistics 3110B. For 9566T, 9566S is a prerequisite. Unless you have either the requisites for this course or written special permission to enroll in it, you may be removed from this course and it will be deleted from your record. Graduate students may do so through the Graduate Chair. This decision may not be appealed. You will receive no adjustment to your fees in the event that you are dropped from a course for failing to have the necessary prerequisites.

Objectives
The purpose of this course is to introduce students to randomized controlled trials (RCTs). RCTs are experiments comparing the effects of different interventions in humans. I will sometimes also use the term ‘trials’, by which I always mean a randomized trial. (Not everyone uses it this way-sometimes others use it to mean non-randomized trial or even an observational study with a comparative purpose- confusing!)

The purpose of the first part of my trial design course is to introduce students to the fundamentals of the RCT design and the crucial advantages this study design offers for evaluation of interventions. The RCT is not “the gold standard” at the top of the design hierarchy for all research purposes; it is merely the least confounded method for evaluating interventions in comparison with each other. But this is not a small advantage, in fact it is a small miracle! And it is due to the act of randomization, so in this course we will pay special attention to what randomization achieves.
(internal validity) and how, and what it does not achieve (external validity) and how we strive for external validity when we need it.

We will also examine randomization and its benefits, as well as the different ways in which we can randomize. We will also discuss units of randomization, as well as the PICOT and other design features, to understand the architecture of the RCT design.

By the end of the 6 weeks comprising the first half of 4715B and all of 9566S students will understand and be able to describe the theory, structure, design and use of randomized controlled trials for evaluation of interventions in human health such as vaccines, drugs, technologies or care, focussed on their internal validity (i.e., their ability to provide, for participants in the trial only, a true estimate of the comparative effect of the tested interventions).

By the end of the second half of the 4715B undergraduate course (cross listed with and same content as 9566T) students will understand and be able to describe the theory, structure, design and use of randomized controlled trials for evaluation of interventions in human health, focussed on their external validity (i.e., the similarity of the effect estimate obtained from participants in the trial to others who are similar to the trial participants and in a similar context but were not part of the trial). To explain this, the second part of my trials design course will introduce you to the concepts of pragmatic and explanatory intentions for RCTs and how to design trials to match one or other of these two intentions. Each intention (also known as attitude) requires a different design and each approach to design should produce a trial with a different purpose. The pragmatic approach is aimed at designing a trial that will provide highly applicable evidence to support a decision on which intervention should be chosen in a specific real-world situation; whereas the explanatory approach is aimed at adding to generalizable basic science knowledge by testing a hypothesis concerning a mechanism of action of an intervention.

Course Organization
Dr. Zwarenstein teaches randomized trial design on Wednesdays in a double class from weeks 1-6 with a coffee break in the middle, and in a single class from weeks 8-13. Synchronous discussion will be in person (and/or on Zoom, depending on pandemic restrictions) on Wednesdays. From weeks 8-13 in the second half of 4715B (and in crosslisted course 9568T), Dr Klar teaches on analysis and statistical issues in RCTs. This is not described here, but will be described in his first session. In this second half, Drs Zwarenstein will teach on pragmatic approaches to trial design in the first half of the double class, and Dr Klar will teach RCT analysis in the second.

There is no assigned textbook for purchase; instead, the reading for each week includes PDFs of selected sections of an out of print textbook: Clinical Epidemiology: How to Do Clinical Practice Research; by Brian Haynes, Dave Sackett, Gordon Guyatt and Peter Tugwell, 3rd edition, LWW publishers, 2006. Readings listed with Chapter numbers or pages only but no title are from these extracts. All readings, including from this textbook, will be found on the OWL course site. Other readings are published papers, also on the OWL course site. All readings, including the published randomized trial papers on which your presentations will be based, will be made available on OWL.

Each class has pre-readings, and a video of a relevant lecture, on the topics listed in the table below, to be studied prior to the in-person class session for which they are listed as pre-video or pre-readings. Video lectures, related readings and self-test, low stakes, two-chance quizzes for Dr Zwarenstein’s classes are on OWL and should be viewed, read and completed in preparation for
each in-person class. The in-class discussion sessions are designed for interaction: questions, presentations and individual and group discussions.

In the first half of the course, the Wednesday in-person discussion class has two parts. The first part is discussion of issues arising from the readings, take-home quizzes and videos completed prior to the lecture. The second consists of in-class student presentations and discussions of issues raised in these presentations. (From the 2nd to the 6th week of the course, each student will give one 5-minute presentation to the class describing and critiquing the randomized trial they selected from the list of COVID-19 RCTs available on OWL). In the second half of the course there are no trial presentations, but in weeks 10 and 13 there will be time for group work on PRECIS-2 and opportunities for volunteers to discuss their work-in-progress on their external validity assignment covering their chosen RCT.

Class Schedule

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<tr>
<th>Date</th>
<th>Topic</th>
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| Wed Jan 11 | **Class:** In person  
Introductions and overview                                              |
| Wed Jan 18 | **Class:** In person  
Architecture of randomization: Parallel, Factorial, Cross-over, Stepped wedge, Clusters. |
| Wed Jan 25 | **Class:** In person  
A: Research Questions, Target Populations, study Population, study Participants: Inclusion and exclusion.  
C: Intervention, Comparator; Placebo and blinding                          |
| Wed Feb 1  | **Class:** In person  
Measurement: Primary, co-primary, secondary, post-hoc Outcomes, Timing, Target.  
The PALSA plus cluster RCT- choice of outcome can matter enormously  
Data collection and organization of RCT  
Cochrane Risk of Bias 2 Tool.                                               |
| Wed Feb 8  | **Class:** In person  
Pilot studies and pilot trials, Qualitative studies, Economic studies alongside trials-  
Ethical issues in design and conduct of RCTs                                |
| Wed Feb 15 | **Class:** In person  
Internal and External Validity  
Bias in Pragmatic Trials  
PRECIS 2 tool: How to make pragmatic or explanatory design choices.         |
| Reading week February 18-26                                              |
| Wed 1 Mar  | **Class:** In person  
Intention (attitude/purpose)  
Domains 1: Eligibility-Who is selected for inclusion in the trial?  
Domain 2: Recruitment-How are they recruited?                                |
<p>| 3:00-4:30  | Analysis: Continuous outcomes                                         |</p>
<table>
<thead>
<tr>
<th>Week</th>
<th>Date</th>
<th>Time</th>
<th>Class</th>
<th>Notes</th>
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| 9    | Wed Mar 8  | 1.30-2.45  | **Class:** In person | **Domain 3:** Setting - Where is the trial carried out?  
**Domain 4:** Organization - What was changed to facilitate the trial?  
Comparator (New domain)                                                                 |
|      |            | 3:00-4:30  | **Analysis:** Binary Outcomes |                                                                 |
| 10   | Wed Mar 15 | 1.30-2.45  | **Class:** In person | Group work                                                             |
|      |            | 3:00-4:30  | **Analysis:** Crossover trials |                                                                 |
| 11   | Wed Mar 22 | 1.30-2.45  | **Class:** In person | **Domain 5:** Flexibility (adherence) - To what extent is behaviour of patients restricted?  
**Domain 6:** Flexibility (delivery) - To what extent is behaviour of intervention providers restricted?  
**Domain 7:** Follow up - How intensively are participants measured? |
|      |            | 3:00-4:30  | **Analysis:** Survival analysis |                                                                 |
| 12   | Wed Mar 29 | 1.30-2.45  | **Class:** In person | **Domain 8:** Primary and Secondary Outcomes - How relevant are outcomes to participants?  
**Domain 9:** Analysis - Are all participants data included?  
Comparison of more Pragmatic and more Explanatory trials of Streptokinase  
Retrospective and prospective use of PRECIS  
Myths about more Pragmatic Trials |
|      |            | 3:00-4:30  | **Analysis:** Interim analysis |                                                                 |
| 13   | Wed Apr 5  | 1.30-2.45  | **Class:** In person | **Coffee, Tea and Timbits**  
Group work  
Discussion of any remaining questions about trials |
|      |            | 3:00-4:30  | **Analysis:** Multiple testing |                                                                 |

**Quizzes:**
Each week (from weeks 1-5 and weeks 9-11) several multiple-choice questions will be assigned for completion. The quizzes can be completed as soon as they are released. They are released on Wednesdays at 4.30 pm for completion before class on the following Tuesday at 11.30 pm. The assessment is automated on OWL: Your first attempt will be instantly graded and returned to you with a clarifying comment. If not correct you have a second shot at the questions with your new grade replacing the first grade. The quizzes contribute to your grade in the first half of the course only. In the second half, although assessed and returned to you with comment, they do not contribute to your grade and are for self-testing purposes only, to help you monitor your understanding of the material.

**Presentations in first half of course:**
As a scientist, whether epidemiologist or a statistician, an important part of your work will involve describing protocols or completed trials and discussing their meaning and methodological reliability with decisionmaker and researcher audiences. You will gain experience of this by presenting a summary of an already published trial to the class during the first half of this course. You should select your trial (which determines the date you will present) by Thursday 12th January as
presentations will begin in week 2. We will provide a list (and PDFs) on OWL – see signup tab- of these published RCTs. If you do not select a trial, one will be assigned to you on Friday 13th January. Each student will present once only, and every RCT will be different. There will be 4 – 6 students presenting their selected RCT on each Wednesday in the first half of the course.

For each of these weeks, the group of students presenting their trials in each week should also meet to discuss the differences between the trials covered by their group in a range of design decisions. Each student in the group will contribute one design choice that differs between their own trial and one or more of the other trials in their group, with an explanation of why they think each of the trials made their choice for that design feature, and what the implications are of their different choices for the findings of those RCTs. students.

First Half Assignment for 4715B (9566S):
Assessing a published trial with the Risk of Bias2 Scale. First assignment on trial design is due Feb 27.

Assignment for second half of 4715 (9568T):
You may choose to do either a design project or the statistical analysis project offered by Dr. Klar. Dr Klar will describe his Analysis Project in class. For Dr Zwarenstein’s design assignment use the PRECIS-2 tool to assess external validity of your RCT. The second assignment is due April 17.

Methods of Evaluation
There will be no exam. The final grade will be made up of several components: online self-test quizzes, a presentation, participation grades, and assignments.

If you are taking 4715B your overall grade (i.e., for both halves) is as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>One Presentation</td>
<td>10%</td>
</tr>
<tr>
<td>Quizzes/Assignments</td>
<td>20% (5 design quizzes. 2 analysis assignments in second half)</td>
</tr>
<tr>
<td>Class participation</td>
<td>20% (first half 10%, second half 10%)</td>
</tr>
<tr>
<td>2 Assignments</td>
<td>50% (first half: design, second half: design or analysis)</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
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For students taking 9566S your grade is as follows:

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<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>One Presentation:</td>
<td>10%</td>
</tr>
<tr>
<td>Quizzes:</td>
<td>5%</td>
</tr>
<tr>
<td>Participation:</td>
<td>10% In discussions, asking questions, proposing ideas</td>
</tr>
<tr>
<td>First half Assignment:</td>
<td>25% Risk of Bias assessment of RCT: design (Due Feb 27)</td>
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<tr>
<td>Total:</td>
<td>50% (x2 =100%)</td>
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For students taking 9568T your grade is as follows:

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<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>2 Assignments:</td>
<td>10% (analysis topics only)</td>
</tr>
<tr>
<td>Participation:</td>
<td>10% (5% Zwarenstein, 5% Klar)</td>
</tr>
<tr>
<td>Final assignment:</td>
<td>30% (Choose either design- Precis 2; or analysis (Due April 17)</td>
</tr>
<tr>
<td>Total:</td>
<td>50% (x2 =100%)</td>
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**Course Materials**
All course materials for Dr Zwarenstein’s section are on the course OWL website.

**Technology Requirements**
You are responsible for all required course materials and announcements posted to the course’s OWL website. Please ensure after the first class that when you log in you are able to access the course site. A copy of the course outline will be available on both OWL and the departmental website. You are also responsible for obtaining access to zoom, with an internet connection and a computer that permits participation in discussion and presentation of your analysis of a published RCT.

**Western Academic Policies and Statements**

**Absence from Course Commitments (Graduate Policy)**
All non-medical absences must be approved in advance. In the case of an unexpected absence on compassionate grounds, documentation may be requested. If documentation is required for either medical or non-medical academic accommodation, then such documentation must be submitted by the student to the instructor.

**Absence from Course Commitments (Undergraduate Policies)**

A. **Absence for medical illness:**
   Students must familiarize themselves with the [Accommodation for Illness Policy](#).

   A student seeking academic accommodation for any **work worth less than 10%** must contact the instructor or follow the appropriate Department or course specific instructions provided on the course outline. Instructors will use good judgment and ensure fair treatment for all students when considering these requests. You are not required to disclose details about your situation to your instructor; documentation is not required in this situation, and you should not send any pictures to your instructor.

   If you are unable to meet a course requirement for any **work worth 10% or greater** due to illness or other serious circumstances, you must provide valid medical or other supporting documentation to the Academic Counseling as soon as possible and contact your instructor immediately. It is the student's responsibility to make alternative arrangements with their instructor once the accommodation has been approved and the instructor has been informed. Please note that the format of a make-up test, exam, or assignment is at the discretion of the course coordinator.

   A student requiring academic accommodation due to illness should use the Student Medical Certificate when visiting an off-campus medical facility or request a Record's Release Form (located in the Dean's Office) for visits to Student Health Services. The form can be found at: [http://www.uwo.ca/univsec/pdf/academic_policies/appeals/medicalform.pdf](http://www.uwo.ca/univsec/pdf/academic_policies/appeals/medicalform.pdf)

B. **Absence for non-medical reasons:**
   Student absences might also be approved for non-medical reasons such as religious holidays and compassionate situations. Please review the policy on [Accommodation for Religious Holidays](#). All non-medical requests must be processed by Academic Counselling. Not all absences will be approved; pay attention to the academic calendar and final exam period when booking any trips.

C. **Special Examinations**
A Special Examination is any examination other than the regular examination, and it may be offered only with the permission of the Dean of the Faculty in which the student is registered, in consultation with the instructor and Department Chair. Permission to write a Special Examination may be given on the basis of compassionate or medical grounds with appropriate supporting documents. To provide an opportunity for students to recover from the circumstances resulting in a Special Examination, the University has implemented Special Examinations dates. These dates as well as other important information about examinations and academic standing can be found here.

**Statement on Academic Offences**

**Undergraduate Policy:** Scholastic offences are taken seriously and students are directed to read the appropriate policy, specifically, the definition of what constitutes a Scholastic Offence, at the following Web site:

http://www.uwo.ca/univsec/pdf/academic_policies/appeals/scholastic_discipline_undergrad.pdf

**Graduate Policy:** Scholastic offences are taken seriously and students are directed to read the appropriate policy, specifically, the definition of what constitutes a Scholastic Offence:

https://www.uwo.ca/univsec/pdf/academic_policies/appeals/scholastic_discipline_grad.pdf

The following policies apply to all students:

All required papers may be subject to submission for textual similarity review to the commercial plagiarism detection software under license to the University for the detection of plagiarism. All papers submitted for such checking will be included as source documents in the reference database for the purpose of detecting plagiarism of papers subsequently submitted to the system. Use of the service is subject to the licensing agreement, currently between The University of Western Ontario and Turnitin.com (http://www.turnitin.com).

Computer-marked multiple-choice tests and/or exams may be subject to submission for similarity review by software that will check for unusual coincidences in answer patterns that may indicate cheating.

**Accessibility Statement**

Please contact the course instructor if you require material in an alternate format or if you require any other arrangements to make this course more accessible to you. You may also wish to contact Accessible Education (AE) at 661-2111 x 82147 for any specific question regarding an accommodation or review the Policy on Accommodation for Students with Disabilities

**Copyright and Audio/Video Recording Statement**

Course material produced by faculty is copyrighted and to reproduce this material for any purposes other than your own educational use contravenes Canadian Copyright Laws. You must always ask permission to record another individual and you should never share or distribute recordings.

**Support Services**

The following links provide information about support services at Western University:

- Academic Counselling (Science and Basic Medical Sciences)
- Appeal Procedures
- Registrarial Services
- Student Development Services
**Student Health Services**

Western is committed to reducing incidents of gender-based and sexual violence and providing compassionate support to anyone who has gone through these traumatic events. If you have experienced sexual or gender-based violence (either recently or in the past), you will find information about support services for survivors, including emergency contacts at [https://www.uwo.ca/health/student_support/survivor_support/get-help.html](https://www.uwo.ca/health/student_support/survivor_support/get-help.html).

To connect with a case manager or set up an appointment, please contact support@uwo.ca.

**Department & Faculty Offices**

The Department of Epidemiology and Biostatistics is located on the third floor of the Western Centre for Public Health & Family Medicine (PHFM) on Western University’s Main Campus.

Undergraduate Students requiring academic counselling should contact the Science & Basic Medical Sciences Academic Counselling Office: [https://www.uwo.ca/sci/counselling/](https://www.uwo.ca/sci/counselling/).

**Cell Phone and Electronic Device Policy**

The Schulich School of Medicine & Dentistry is committed to ensuring that testing and evaluation are undertaken fairly across all our departments and programs. For all tests and exams, it is the policy of the School and the Department of Epidemiology and Biostatistics that any electronic devices, i.e., cell phones, tablets, cameras, or iPod are strictly prohibited. These devices MUST be left either at home or with the student’s bag/jacket at the front of the room and MUST NOT be at the test/exam desk or in the individual’s pocket. Any student found with one of these prohibited devices will receive a grade of zero on the test or exam. Non-programmable calculators are only allowed when indicated by the instructor. The Department of Epidemiology and Biostatistics is not responsible for stolen/lost or broken devices.