

UTOPIAN Clinical Research Group Meeting MINUTES

January 27, 2022
Time: 4:00 PM – 5:00 PM EST
Teleconference (Zoom)

Action Items:

1. Members can visit the DFCM YouTube channel at a later time for self-learning and other videos:
<https://www.youtube.com/c/UniversityofTorontoFamilyMedicine>
2. For those interested, the registration deadline for CIHR project grants is on **February 09, 2022**, and the full application is due **March 09, 2022**.
3. For those interested in a long COVID-19 study, please contact Dr. Andrew Pinto at,
andrew.pinto@utoronto.ca

Review & Approval of Minutes

- Minutes from the previous UTOPIAN Clinical Research Group (CRG) meeting were **approved**.

CRG Lecture Series Plan Update

- This lecture series will be recorded and made available on YouTube. The goal is to work towards an article series about conducting clinical trials in primary care aimed at a submission to the Annals of Family Medicine as the journal is interested in publishing more audio-visual content.
 - Lectures may be re-recorded prior to submission, so members are encouraged to provide feedback on how they can be improved and if any content can be added, removed, or changed.
- Current topics include:
 - Introduction of clinical trials in primary care (Dr. Andrew Pinto | January 27)
 - Patient oriented clinical trials in primary care (Dr. Michelle Greiver | February 24)
 - Recruitment challenges and solutions in primary care trials (Speaker TBD | March 31)
 - Common approaches to analyzing data from clinical trials in primary care (Dr. Rahim Moineddin | April 28)
 - Ethical considerations for trials in primary care (Dr. Ross Upshur | May 26)
 - Regulatory requirements for clinical trials in Canada and the U.S. (Speak TBD | June 30)
- A potential additional topic is 'Tips to applying to the Canadian Institutes of Health Research (CIHR) grants.' by Dr. Andrew Pinto.

Lecture Series 1: Introduction of Clinical Trials in Primary Care

Presenter. Dr. Andrew Pinto

What are RCTs?

- Randomized controlled trials (RCTs) are one form of evaluative research design that addresses whether and to what extent interventions achieve their intended outcomes.
- To test an intervention, RCTs involve randomly allocating participants to an intervention or control group(s). The comparison/control groups do not receive the intervention but are alike to the intervention group in all other ways.
- Examples of interventions include new or innovative medications, devices, vaccines, and new programs and services, etc.

Why do RCTs?

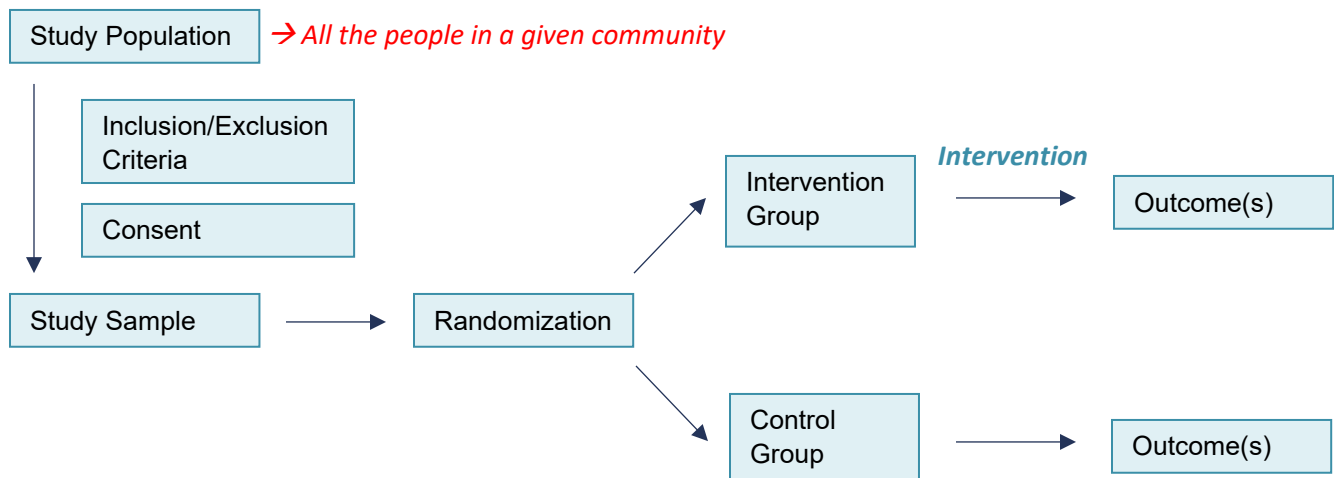
- In research, a common struggle is knowing if an intervention is truly effective, and as a research design, RCTs are a tool that can help determine whether the intervention had an impact beyond other influencing factors, including characteristics, attitudes, and perspectives of participants and/or the research team, and changing social contexts.
 - This reduces chances of being misled about an interventions impact and allows the research team to make statistical statements about the probability that the results were by chance.

Randomization

- Randomization involves randomly placing people in the intervention or control group(s) to address selection bias.
- If people chose which group they were allocated to, it would limit the ability of the study to determine whether any impact was due to the intervention or other factors influencing the outcome (i.e., the composition or motivation of participants in each group).

RCTs: Parallel Group Design

- A common diagram seen in research is the RCT parallel group design:



- Randomization can occur through a variety of methods (e.g., via online software, sheets of paper, a randomization sequence, etc.), however ultimately, everyone in the study sample has an equal chance of being in the intervention or control group.

Outcomes

- By nature, RCTs follow people forward in time and evaluate a **pre-specified outcome** that the research team feels will be influenced by the intervention (e.g., risk of heart attack).
- There is an assumption that the difference in the primary outcome is the only difference between the intervention and control group(s).

Strengths of RCTs

- RCTs address questions about efficacy, and in the ideal setting, allow teams to think about causation.
- RCTs have high internal validity in that the differences between the intervention and control group(s) can be attributed to the intervention. The study design minimizes bias and balances unknown and known confounding variables that could account for changes in the outcome.
- There is control over how much exposure to the intervention participants get, and who gets it.
- RCTs also involve standardized data collection, allowing for clean data.

Limitations of RCTs

- One of the issues with RCTs is their high cost, often due to the energy required to recruit sufficient participants, consent, collect data, and follow people over time.
 - Due to this and the size of RCTs, there tends to be a shorter follow-up period vs. other designs.
- There are also limits to external validity (i.e., being able to generalize findings), as the study is conducted in a tightly controlled setting.
- By their nature, RCTs provide an intervention to one group of people and not to another. This introduces ethical concerns about whether the controls are being denied an intervention that could be beneficial.
- Small sample sizes may miss rare or delayed outcomes.

Types of RCTs

- Other types of RCTs include:
 - Cross-over design: One group gets the intervention and then there is a 'washout period' where neither group gets the intervention, followed by the other group getting the intervention.
 - Factorial design: Groups get different measures of the intervention or control.
 - Pragmatic RCTs: Try to test interventions in as 'real' in a situation as possible.
 - Pilot RCTs: Focused not on being powered to detect a significant difference but rather on testing the design/feasibility of the study (i.e., can you recruit people, can you consent people). These may generate initial data that can help calculate sample sizes for a larger study.
 - Cluster RCTs: The intervention is delivered at a group level (i.e., a small community, or clinic). For example, different clinics as a whole are randomized to the intervention or control group(s).
 - Stepped wedged cluster RCTs: The intervention is delivered ultimately to the whole clusters, but **when** people get the intervention is randomized.

Steps in a RCT

1. Forming a research team
 - a. Includes a study lead, site investigators who are responsible for site recruitment, biostatistical support, and staff to collect data and conduct the write up.
 2. Finalizing a research question & PICOT
 - a. PICOT: population, intervention, control, outcomes, timeline
 3. Defining inclusion and exclusion criteria
 4. Planning for randomization
 5. Defining and delivering the intervention and deciding on the control
 6. Outcomes & analysis plan
 7. Sample size calculation
 8. Blinding and addressing bias
 9. Data collection, analysis, and dissemination
- When thinking about a research project, providing even initial answers to these questions can help develop a research idea and grant proposal. Most grant agencies ask questions related to these areas.
 - A CONSORT diagram is required when reporting on studies but is also helpful to visualize how different parts of the study will take place (i.e., from enrollment to allocation, to follow-up and finally to analysis).

When are RCTs Not Possible?

- When an intervention is given to an entire population, making randomization impossible.
- In some situations, it is unethical to conduct an RCT. For example, the intervention may be harmful.
- An alternative to RCTs is a quasi-experimental design in which researchers look at who received an intervention and try to match controls that have similar characteristics and but did not receive the intervention.

RCTs and Real-World Application

- RCTs are often conducted in a highly controlled environment and so a prominent concern is whether they are generalizable to the broader population.
 - RCTs are often seen as the gold standard type of evidence, however multiple types of studies and research designs are required to come to a definitive conclusion of an intervention's efficacy and application to individual patients.

Discussion

- The presentation sums up RCTs effectively and hits key aspects of their design.
- Suggestion to include an additional slide that links published RCTs that are exemplary in their design and have had a tangible impact in primary care.
 - It is possible to also pick an example RCT and incorporate it throughout the presentation to illustrate various design elements.
 - Eg, Sullivan et al, 2007, Early treatment with Prednisolone or Acyclovir in Bell's Palsy (<https://www.nejm.org/doi/full/10.1056/nejmoa072006>); Butt et al, 2008, Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial (<https://pubmed.ncbi.nlm.nih.gov/17917611/>)

Major Clinical Trials Update

SPIDER

- Recruitment in Ontario has exceeded targets (14 sites) and is still ongoing.
 - The project has been identified as a qualified QI project in CPSO's practice improvement plan.
- The project is seeking additional funding.
 - SPIDER has been accepted as a keystone project in a CIHR Primary Care Network grant application that is offering \$10M over 5 years.
 - The project has secured a \$1.5M match from a variety of partners and brought on two additional provinces (British Columbia and Newfoundland).

SPARTAN-AD

- Recruitment is ongoing and various strategies have been implemented to overcome initial challenges. Primarily, a primary physician or nurse will now make the initial contact with patients to build trust, following which the project research officer will engage in the recruitment process.
 - This highlights that early input from UTOPIAN can help studies achieve their project goals.

Recent Publications

- Crampton N, Greiver M, Woods N, Singer A, Domb S, Orava M, Shachak A. [Teaching electronic medical record \(EMR\) data discipline to clinical trainees: A Canadian pilot study](#). International Journal of Medical Informatics, 2022. 159.
- O'Neill B, Kalia S, Gill P, Hum S, Moran-Venegas C, Stoller R, Greiver M, Agarwal P, Kirubarajan A, DeKoven S, Eisen D, Pinto A, Dunn S. [Association between new-onset anosmia and positive SARS-CoV-2 tests among people accessing outpatient testing in Toronto, Ontario: a retrospective cross-sectional study](#). CMAJ Open. 2021 Dec 7;9(4):E1134-E1140. doi: 10.9778/cmajo.20210085.
- Walji S, McIsaac W, Moineddin R, Kalia S, Levy M, Tu K, Bell CM. [Predicting hospital readmission risk: A prospective observational study to compare primary care providers' assessments with the LACE readmission risk index](#). PLoS One. 2021 Dec 15;16(12):e0260943. doi: 10.1371/journal.pone.0260943.

New Research Ideas

- Treatment of long COVID in primary care: There are currently no treatments for long COVID-19 and primary care is likely where this illness will be addressed. A proposal is being put together to study

treatments for long COVID-19, which will ideally include an interdisciplinary team of primary care, rehabilitation, physiatry, and internal medicine.

- To connect with Andrew if interested in getting involved
 - Dr. Noah Crampton is involved in a long COVID trial led by GIM at UHN
- Suggestion to contact family medicine residents if they would like to get involved in a study during its early stages.