The CONTROL

(COgNitive Therapy for depRessiOn in tubercuLosis treatment)

to improve outcomes for depression and TB in Pakistan and Afghanistan

Funded by: RIGHT3, NIHR

Reference: NIHR201773

"WORKSHOP ON CONDUCT

&

MANAGEMENT OF RANDOMIZED

CONTROLLED TRIALS"

7th November 2023

Drafted by: Dr. Saima Aleem

Reviewed by: Dr. Zohaib Khan

EXECUTIVE SUMMARY

Capacity development is an integral component of the CONTROL study as the research team comprises early careers researchers as Research Assistants, qualitative and quantitative researchers, data input administrators, Ph.D. students, and Post Doc fellows. Recognizing that robust capacity development needs and developing a holistic approach empowers team members to bring a higher level of expertise, efficiency, and a constructive mindset to their work, ultimately enhancing the overall success and impact of the project.

The "Conduct and Management of Randomized Controlled Trial" workshop, conducted on 7th November 2023 in Islamabad, was a specialized training program designed to address the intricate aspects of planning, executing, and overseeing randomized controlled trials (RCTs). Acknowledging the critical role RCTs play in shaping evidence-based practices, this workshop aimed to equip participants with the knowledge, skills, and tools necessary to navigate the complexities of trial design, implementation, and management.

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INTRODUCTION

Workshop Background:

Under the umbrella of the CONTROL Global Mental Health Symposium scheduled for 8th & 9th November 2023, a pre-symposium workshop was planned for the research team of CONTROL and representatives from the global mental health projects being conducted from Khyber Medical University.

Objectives of the workshop

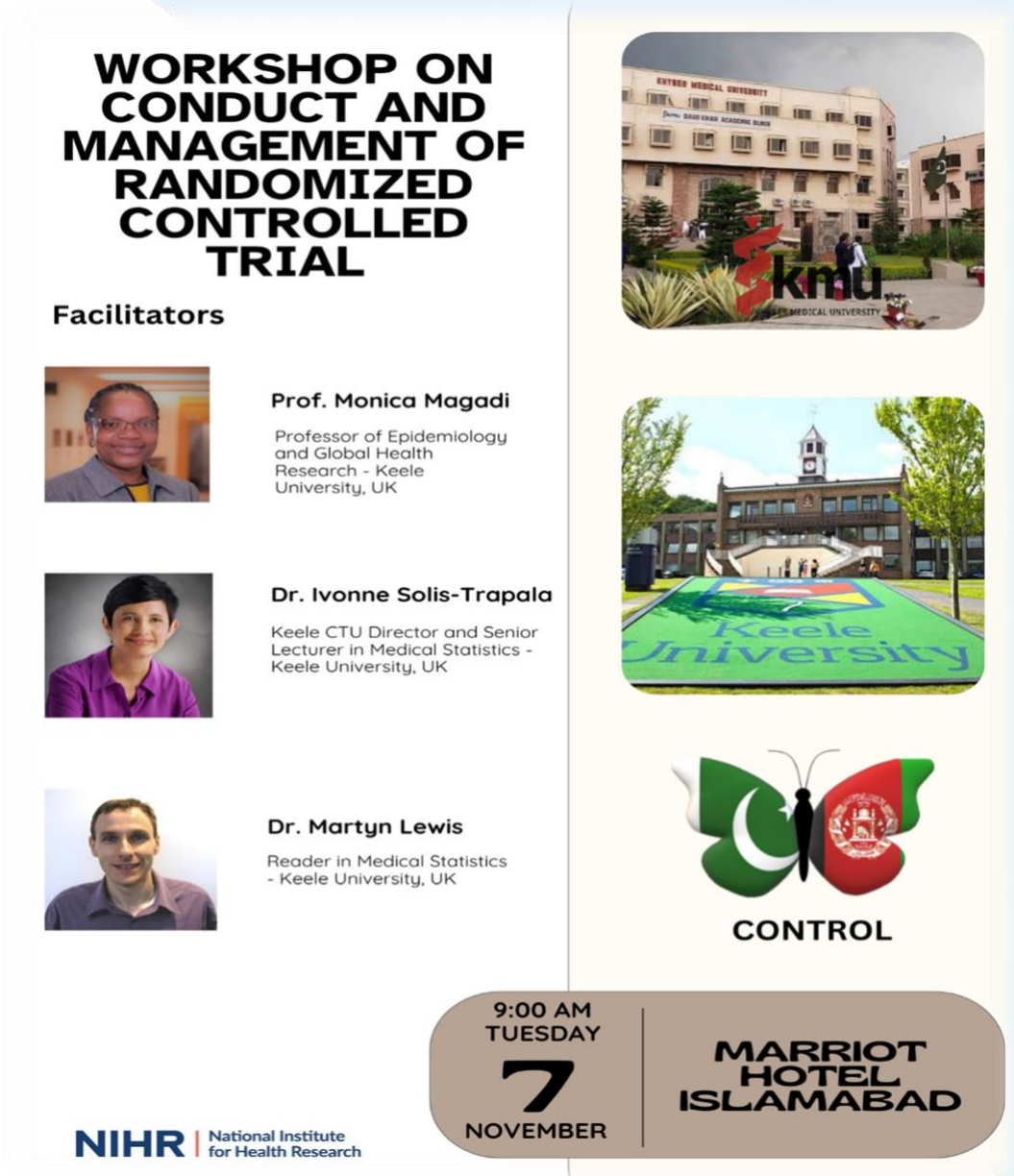
1. Prioritize the development of core research and clinical trials-related competencies, including trial designs, data collection, analysis, and interpretation, to empower participants with a well-rounded skill set.
2. Provide participants with a solid foundation in the key elements of randomization, blinding, and control groups.
3. Equip participants with the skills necessary to conduct appropriate statistical analyses for RCT data.
4. Guide participants in interpreting and communicating RCT results effectively.
5. Discuss best practices for reporting findings following clinical trial reporting standards and guidelines.

Participants:

The workshop was CONTROL PIs, research team, Ph.D. students, Post Doc Fellows, representatives, and research team members from the NIHR-funded DiaDem study, THE HOPE study, and Pakistan Higher Education Commission-funded POTENTIAL study.

Workshop facilitators:

The workshop was facilitated by:



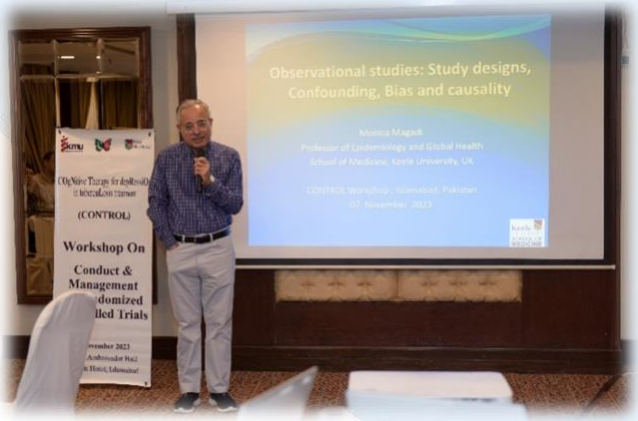
Workshop proceedings

The workshop commenced with a recitation of the Holy Quran by Dr. Fayaz Ahmad. Dr. Zohaib Khan extended a warm welcome to the diverse assembly of early and mid-career researchers, academicians, and professionals convened for the collaborative learning

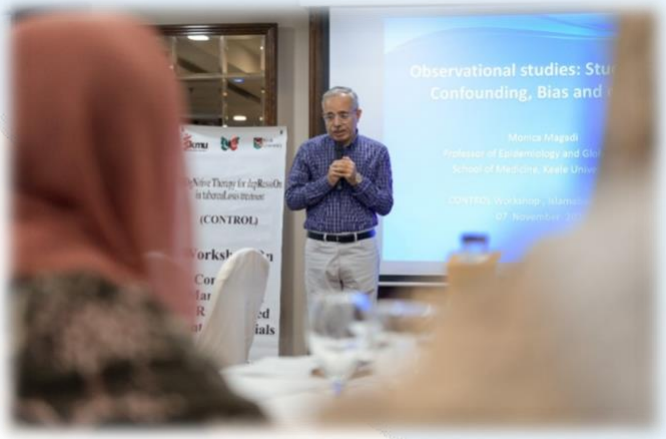
experience and expressed gratitude for the facilitators and participants' commitment to advancing their knowledge and skills in the subject matter.

Following the introductory remarks, a round of participant introductions ensued. This initial exchange of information fostered an atmosphere of camaraderie and set the stage for meaningful interactions throughout the workshop.

CONTROL study overview:



Prof. Saeed Farooq first extended his gratitude to the three facilitators for traveling from the UK to conduct the workshop and appreciated their commitment to capacity development. He also mentioned the contribution of the CONTROL team at Keele University. Prof. Saeed mentioned that the inception of the CONTROL study emanated from the recognition of the escalating complexities inherent in mental health phenomena especially among Tuberculosis patients and a resolute commitment to fostering innovative approaches to address these challenges. At the same time, the interdisciplinary nature of our team, comprising esteemed researchers, clinicians, and experts in various facets of mental health and tuberculosis, forms an integral aspect of the study's strength. Each team member brings a wealth of experience and specialized knowledge to the table, collectively contributing to the holistic understanding of our research objectives. He extended his sincere appreciation to each team member for their dedication, expertise, and collaborative spirit.



Prof. Saeed highlighted that the CONTROL study methodology is anchored in meticulous research design, encompassing both quantitative and qualitative approaches to capture the multifaceted dimensions of research. The utilization of advanced assessment tools, coupled with rigorous data analysis methodologies, reflects our commitment to ensuring the integrity and validity of the findings.

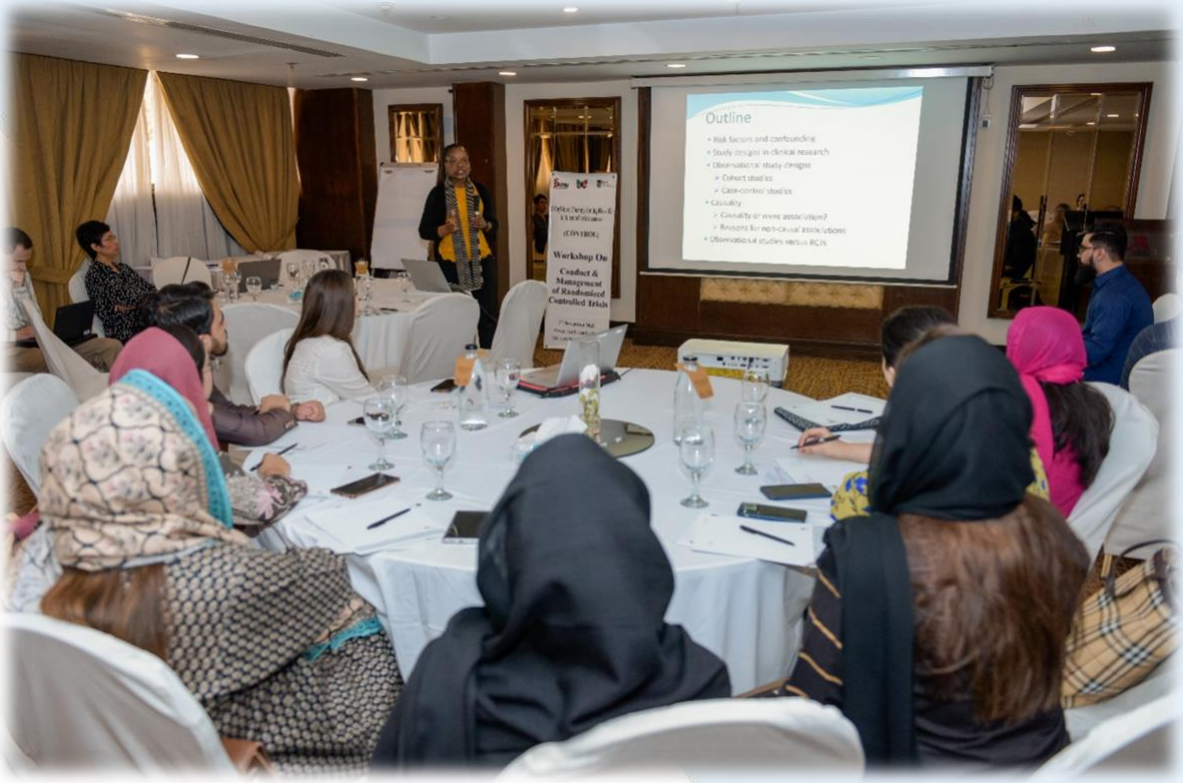
Furthermore, ethical considerations stand as a paramount cornerstone of this study. We are unwavering in our commitment to safeguarding the well-being and confidentiality of our participants. Our research protocols adhere rigorously to institutional and international ethical standards, underscoring our dedication to the responsible conduct of research.

Prof. Saeed expressed his utmost confidence that the collective and collaborative efforts will yield outcomes that transcend the boundaries of academic discourse and will serve both local Pakistani and Afghan refugees in dire need of integrated health care for TB and depression.

Session 1:

Observational studies: Study designs, Confounding, Bias, and Causality

Prof. Monica Magadi, Professor of Epidemiology and Global Health, School of Medicine, Keele University, UK facilitated the first session of the workshop.



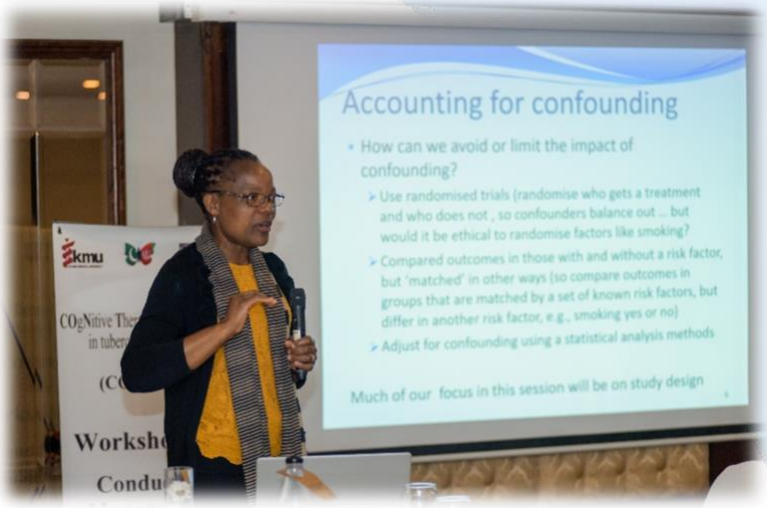
The outline of Prof. Monica's session was:

- Risk factors and confounding
- Study designs in clinical research
- Observational study designs
    - ➢ Cohort studies

- Case-control studies

- Causality
  - Causality or mere association?
  - Reasons for non-causal associations

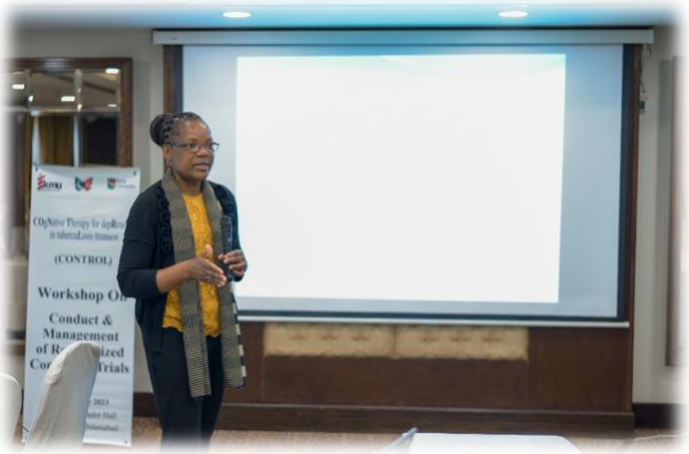
- Observational studies versus RCTs



Prof Monica mentioned that a common interest in epidemiological studies is to identify factors that are associated with an outcome of interest (e.g., disease) and these are often termed ***risk or prognostic factors.*** When observing the association between two variables (which are usually an exposure of interest and an outcome of interest, e.g., alcohol and cancer incidence; location and death rate), a confounding factor is a third variable that is associated with both these two variables, and thus may cause an artificial (non-causal) association to be observed between these two variables. She explained that there are different ways of accounting for confounding including:

- Appropriate study design (randomization, matched pairs)
- Statistical analysis (e.g. regression)

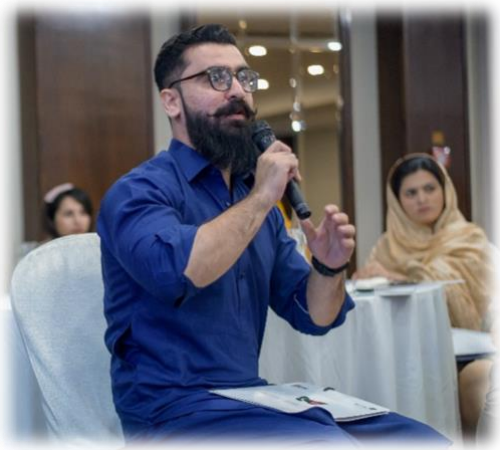
Study design: Appropriate study design is crucial to enable meaningful examination of risk factors of specific disease conditions: from sample selection to patient recruitment; to collection of suitable data; and application of appropriate statistical methods to identify risk factors.



Clinical research falls into two general categories: experimental and observational, based on whether the investigator assigns the exposures or not. Experimental trials can also be subdivided into two: randomized and non-randomized. Observational studies can be either analytical or descriptive. Analytical studies feature a comparison (control) group, whereas descriptive studies do not. Within analytical studies, cohort studies track people forward in

time from exposure to outcome. By contrast, case-control studies work in reverse, tracing back from outcome to exposure. Cross-sectional studies are like a snapshot, which measures both exposure and outcome at a one-time point. Descriptive studies, such as case-series reports, do not have a comparison group.

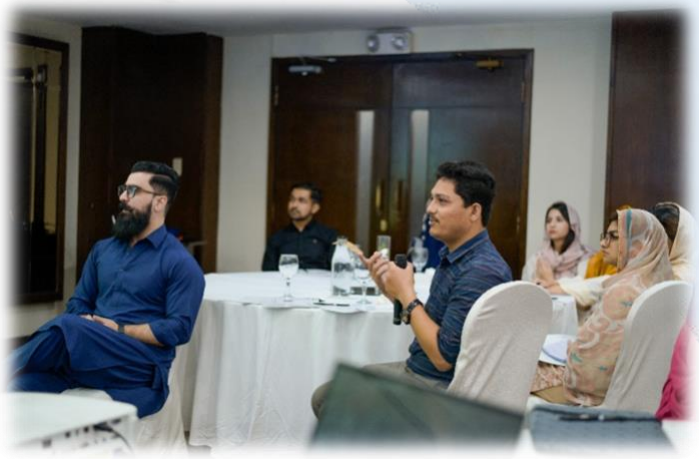
Confidence intervals around these measures indicate the precision of these results. Measures of association with confidence intervals reveal the strength, direction, and plausible range of an effect as well as the likelihood of chance occurrence.



The detailed explanation of core concepts was followed by a question-answer session regarding all study designs, their pros and cons, and what exact statistical methods are employed across different study designs, Prof. Monica briefed the participants about risk factors and causes, causal and non-causal associations, chances, and bias.

She mentioned that Non-Causal Associations can arise in several ways:

- By chance,
- Because of bias
- Because of confounding
- Through reverse-causality



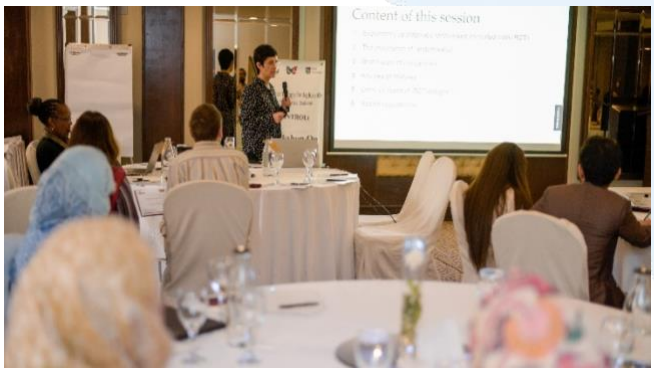
She concluded the session by highlighting that both observational studies and randomized controlled trials (RCTs) are commonly applied and fulfill a complementary and valuable role in clinical research. Furthermore, RCTs largely depend on work from preceding observational studies – e.g. estimation of effect size for sample size determination. However, researchers and users of evidence from epidemiological studies should be aware of the specific qualities, strengths, and limitations of each study design.

In general, RCTs are the optimal study design to study the effects of therapy or other interventions and to establish causality, although their use is limited by ethical and practical concerns. Conversely, observational study designs, including case reports, case series, cross-sectional studies, case-control studies, and cohort studies, are usually more useful than RCTs for non-therapeutic research questions.

Session 2:

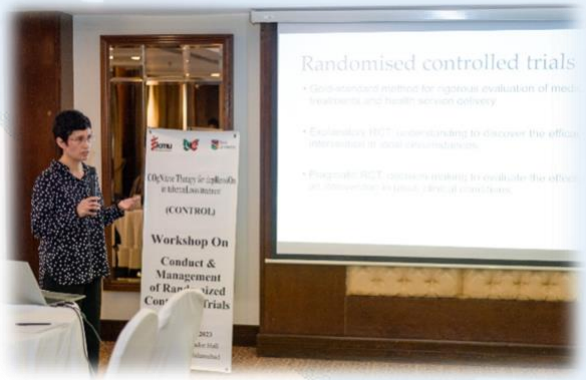
Randomized Controlled Trials:

Session 2 was facilitated by Dr. Ivonne Solis-Trapala, Keele CTU Director. She first appreciated and acknowledged the efforts of Prof. Saeed Farooq, Dr. Zohaib Khan, Dr. Zeeshan Kibria & Ms. Saima Sheikh for coordinating and arranging the workshop.



The outline of Dr. Ivonne's session included:

1. Explanatory *vs* pragmatic randomised controlled trials (RCT)
2. The importance of randomisation
3. Brief history of clinical trials
4. Key design features
5. Common types of RCT designs
6. Reporting guidelines



Prof. Ivonne mentioned that randomized controlled trials are a gold-standard method for rigorous evaluation of medical treatments and health service delivery. Explanatory RCT deals with the understanding to discover the efficacy of an intervention in ideal circumstances where whereas Pragmatic RCTs are decision-making to evaluate the effectiveness of an intervention in usual clinical conditions.

If A and B are clearly associated, positively with statistical significance

A ——— B

It may be that:

a) A is an important cause of B

A ⟶ B

b) B is an important cause of A

A ⟵ B

c) Something else say X, is an important cause of both

A ⟵ X ⟶ B

Randomisation Z, excludes b) and $X \longrightarrow A$, we know that $Z \longrightarrow A$,

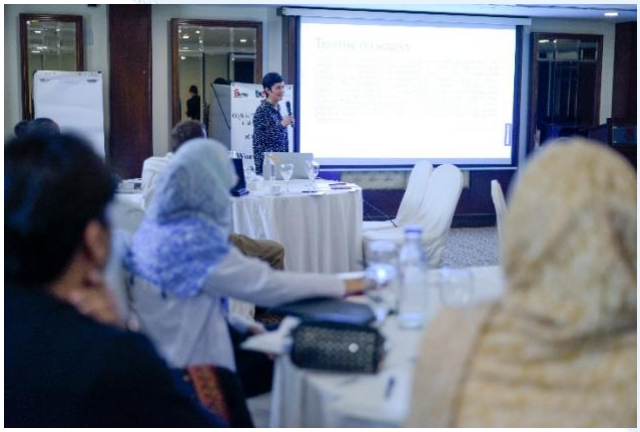
it follows that:

Z ⟶ A ⟶ B

X ⟶ B

She explained the concept of how randomization works as projected below.

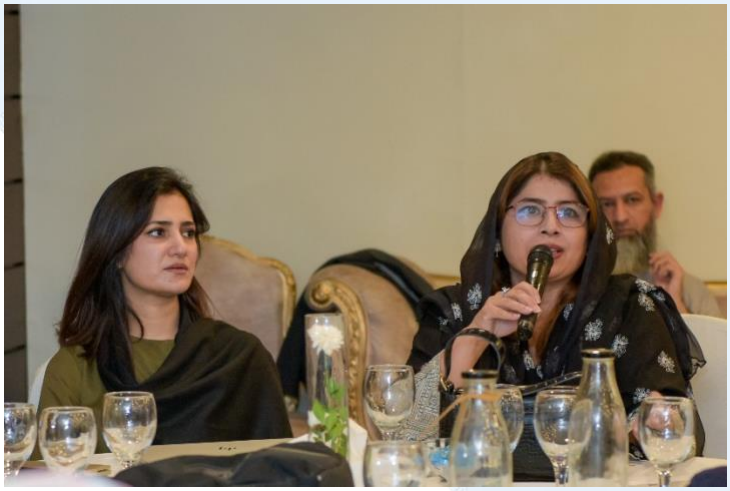
This was followed by highlighting the core concept of Bradford Hill's criteria of causality as in epidemiology, this is used as evidence to support a causal association:



- Plausibility (reasonable pathway to link outcome to exposure)
- Consistency (same results if repeat in different time, place person)
- Temporality (exposure precedes outcome)
- Strength (with or without a dose response relationship)
- Specificity (causal factor relates only to the outcome in question - not often)
- Change in risk factor (i.e. incidence drops if risk factor removed)

Next, she explained the phases of clinical trials:

1. Tolerability and Toxicity (*e.g.* absorption, metabolism, excretion of drug)
2. Potential efficacy *e.g.* dose-finding, safety
3. Randomised Controlled Trial (Full-scale evaluation of the effectiveness of a new experimental treatment to standard therapy or placebo)
4. Post-marketing surveillance (*e.g.* to identify uncommon side effects, rare adverse reactions, long-term effects).



Dr. Ivonne was asked about the key design elements to be considered while dealing with RCT to which she elaborated that PICO should be the key where **P** is the population who are to be targeted, **I** is the intervention that you want to do for patients, **C** is the comparison that is there a control group or alternative treatment to compare the intervention with, and **O** is the outcome that what do you intend or hope to improve in patients.

Complex interventions:

Prof. Ivonne shared the concept of complex interventions and mentioned that an intervention is considered complex when it comprises multiple interacting components, involves diverse groups or levels of stakeholders, and requires a nuanced and adaptable implementation process. Several factors contribute to the complexity of an intervention:

- Interacting components within experimental and control interventions
- Behaviours of those delivering or receiving the intervention
- Complexity at the organizational level in delivering the intervention.
- Number and variability of outcomes
- Flexibility in tailoring of the intervention is allowed.

Pilot and feasibility studies:

Prof Ivonne briefed about the importance of pilot and feasibility studies and mentioned that a pilot feasibility study is a valuable step in the research process, offering insights, minimizing risks, and improving the overall quality and success of the subsequent larger-scale study.

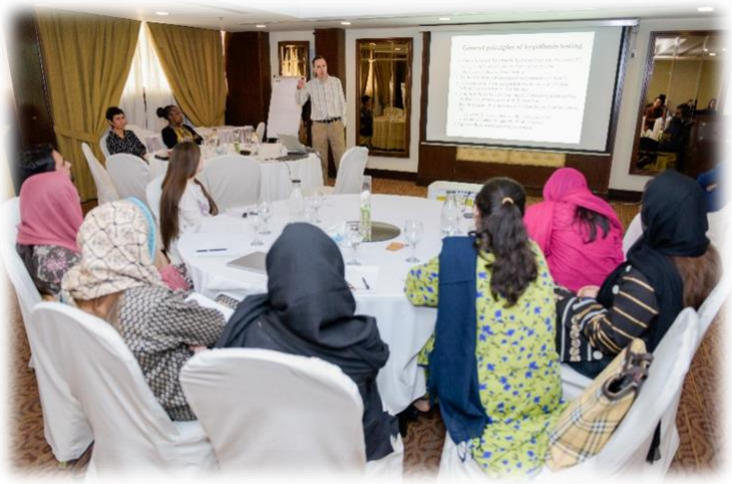
These studies are an important pre-requisite for funding especially for multi-centre studies and allow researchers to identify potential problems or challenges or uncertainties in the study design, procedures, or data collection instruments and help in refining and optimizing the research protocol based on practical experiences and feedback from participants.

Session 3:

Randomized Controlled Trials:

Session 3 was facilitated by Dr. Martyn Lewis, Readers in Statistics at Keele University UK. His session focused on statistical methods in clinical trials including sample size and analysis.

Descriptive and Inferential Statistics:



Descriptive statistics are used to summarize and describe the main features of a sample and dataset. They provide a clear and concise summary of the essential characteristics of the data, helping to make the data more understandable and interpretable, whereas **Inferential statistics**

involve making inferences and predictions about a population based on a sample of data. The goal is to draw conclusions that extend beyond the immediate data and to make generalizations or predictions about a larger population.

Both types of statistics are essential for understanding and drawing meaningful insights from data in various fields, including science, business, and social sciences. This was followed by the giving the workshop participants orientation about the variables and their types.

The segments covered by Dr. Martyn in the initial orientation session were:

- Graphical presentation of data
- Summary measures
- General principals of hypothesis testing
- Errors associated with hypothesis testing.

Choosing the right method of analysis:

Dr. Martyn mentioned that choosing the right method of analysis is fundamental to the success of your research. It ensures the accuracy, reliability, and validity of your findings, aligns with your research objectives, and facilitates effective communication of results to both the scientific community and the broader audience. Researchers should carefully consider their data, research questions, and study design when selecting an appropriate analysis method.

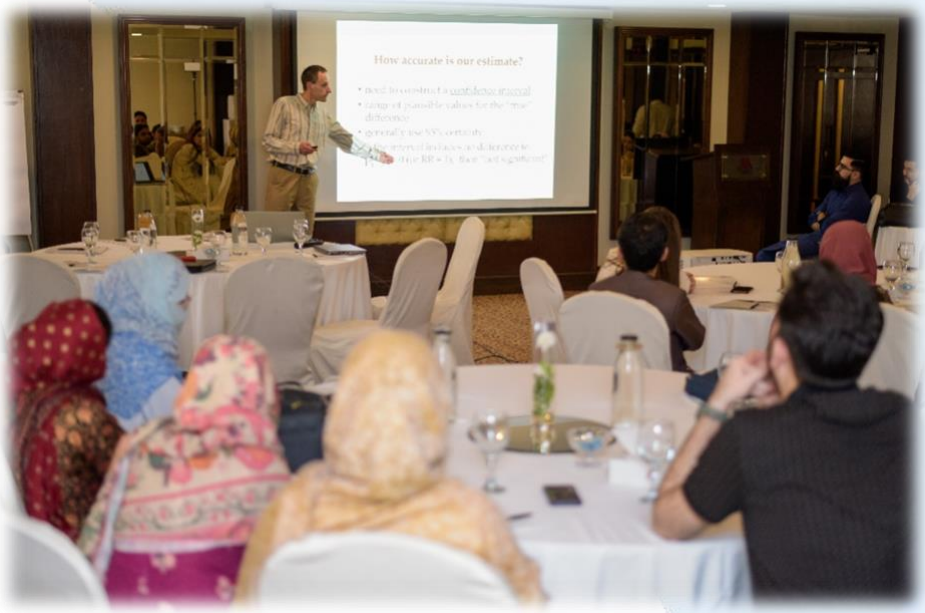
In the next half of the session, he discussed the sample size estimation and statistics involved in data analysis.

Health Economics:

There are different types of health economics analysis:

- Cost consequence analysis: examines costs and consequences broadly (over several measures) and in disaggregated form

- Cost minimization analysis (CMA): consequences are assumed to be equivalent; only costs are compared
- Cost-effectiveness analysis (CEA): consequences are measured in natural units (for cost-utility (CUA) this is quality-of-life-years (QALYs)) and compared versus costs



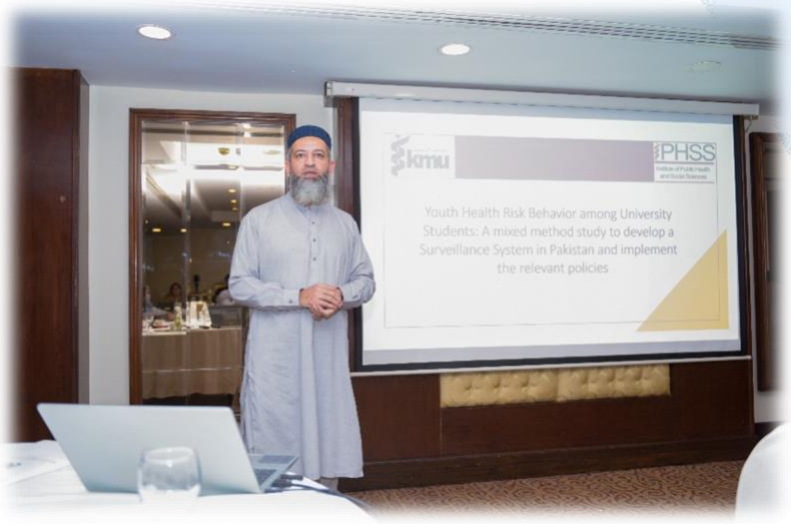
- Cost-benefit analysis (CBA): consequences are valued in monetary units.

Dr. Martyn discussed in detail the various aspects of this analysis with examples from published literature for a better understanding of workshop participants. The session ended with a comprehensive question-answer session.

Session 4:

Post-Doc Fellow Project Showcase:

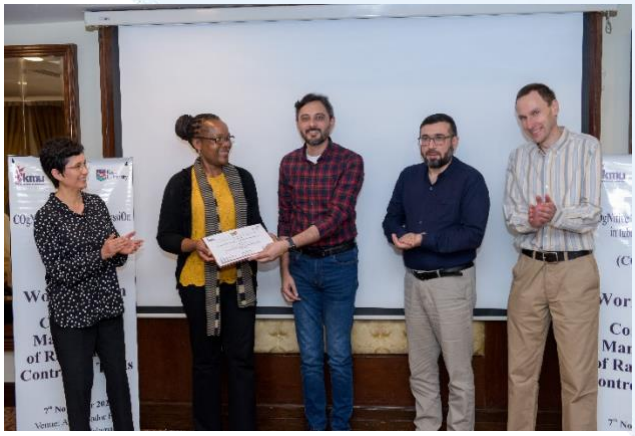
Dr. Fayaz Ahmad and Dr. Shaista Rasool, Post-doc fellows in CONTROL showcased the two proposed projects based on their own professional expertise and research interests. Dr. Shaista discussed the extension of her own Ph.D. research to the implementation level.

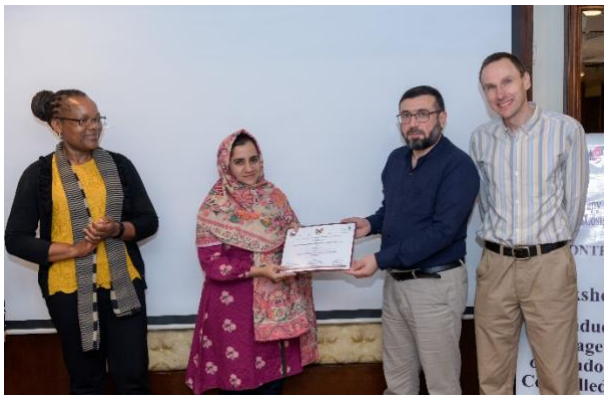


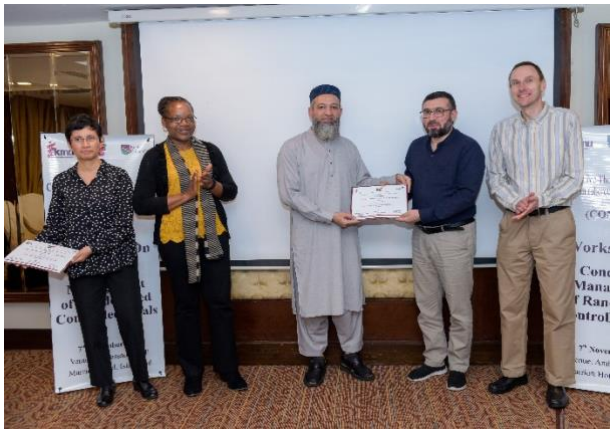
Dr. Fayaz discussed the youth health risk behaviour survey among university students in Khyber Pakhtunkhwa. Both research projects were innovative and inspiring for the workshop participants as they motivated them to bring their research concepts to reality by taking the initial step to drafting and presenting their research proposals.

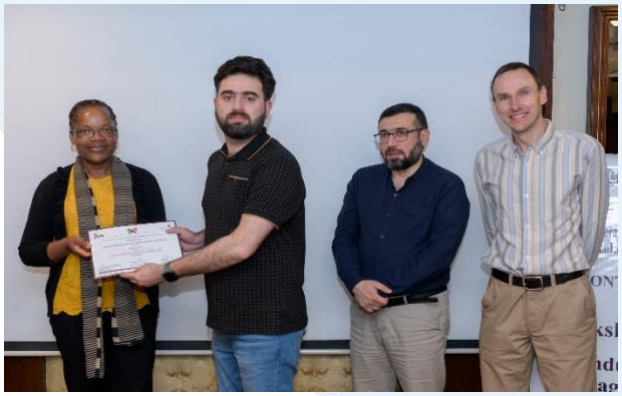
Closing Session:

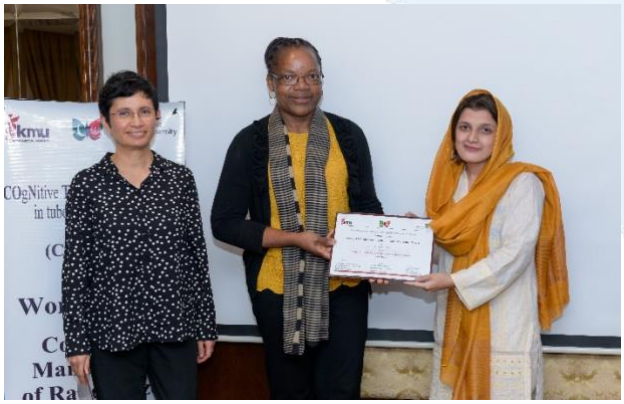
The workshop closed with a vote of thanks from Dr. Zohaib Khan to all the facilitators and workshop participants followed by certificate distribution and group picture.

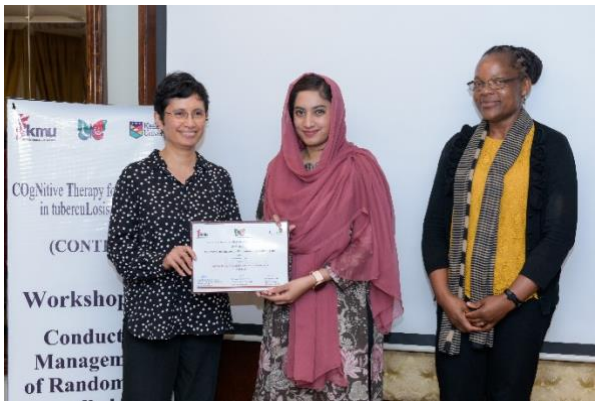


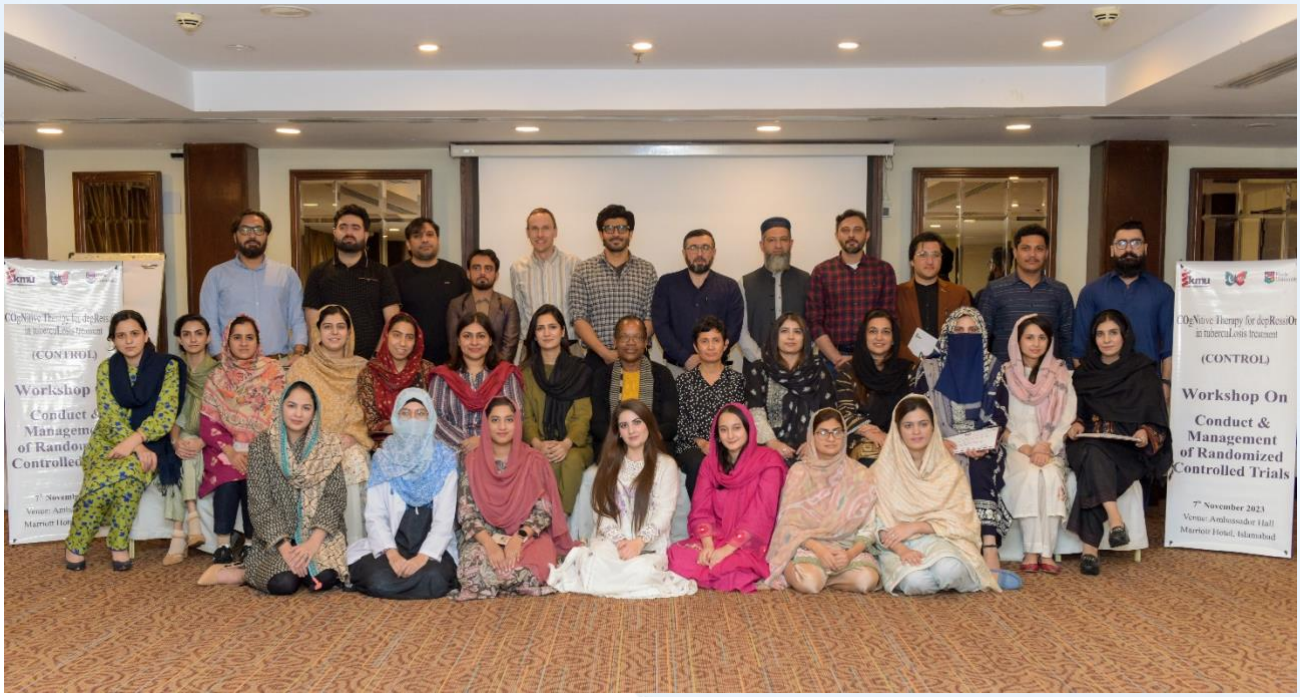












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