Ethical Issues in Randomised Clinical Trials for Adolescents who Self-Harm: The limits of equipoise and evidence in the cultural context of Pakistan

“It is uncertainty or equal belief that there is equal balance between the two treatments in the trial and that one is equally effective than the other”.

Benjamin Freedman 1987

Rakhshi Memon
UCL Department of Science and Technology
PhD in Bioethics
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Dedication

To my late parents (Retd.) Major General Dr Ishrat Husain and Mrs Noor Jehan Begum who were great advocates of life-long learning; they gave me the self-belief that if you really want something, you make the impossible possible.

Acknowledgements

I would like to express my appreciation and gratitude to my brother Professor Nusrat Husain who inspired me to embark on this journey. To my supervisor, Professor Sarah Edwards who has been my rock throughout the process, I am grateful for her endorsement and faith in my abilities whenever my confidence dwindled. To my 2nd supervisor, Dr Alexandra Pitman for her support and guidance particularly on the methods section. My mentors, Professor Nasim Chaudhry and Professor Imran Chaudhry for their help and encouragement, Pakistan Institute of Living and Learning (PILL) for funding my PhD, the PILL team and in particular Muqaddas Asif for her cooperation and support as and when I needed it. My neighbour, Neil Munro for proofreading my thesis, diligently going through it with a fine tooth comb and last but not least my husband Yahya and my sons Farhan and Ahmer without their backing and reassurance I could not have completed this journey.
Declaration

I, Rakhshi Memon confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

_________________
Rakhshi Memon
Abstract
This research examined the main conceptions of equipoise and applied them in a different cultural context based on a Randomised Clinical Trial (RCT) being conducted in Pakistan, which is investigating a psychological intervention YCMAP plus treatment as usual versus treatment as usual for young people at risk of self-harm or suicide. Equipoise is the moral justification for recruiting participants in an RCT, when there is uncertainty about which arm of the trial is more beneficial to the patient. The current research focused on whether the clinicians’ recruiting patients have a treatment preference and whether they regard participation in an RCT as scientifically and ethically important.

Methods
The study used an exploratory mixed methods approach; survey of clinicians, both involved and not involved in the trial and a discussion group with Pakistani researchers. It included an empirical study of the views and values of clinicians (N=20). The study examined the ethical considerations regarding clinical trials and human rights law. My thesis reviewed literature on Islamic approaches to research ethics, developed a community engagement tool for use by western researchers through a discussion group with Pakistani researchers and conducted semi structured qualitative interviews with the clinicians to explore the cultural context.

Results
Findings showed that clinicians (73.3%) consider YCMAP to be an effective treatment for young patients at risk of self-harm or suicide. Although, there was acknowledgement of individual preferences, there was greater consensus on the need to conduct an RCT for reaching an evidence-based decision.

Conclusion
From my research, I conclude that there was enough evidence of uncertainty and the existence of clinical equipoise as moral justification for conducting the RCT. There was a desire to gather home grown evidence base to make it more culturally relevant. Religiosity was a dominant thread across all the themes from the cultural analysis.
Impact Statement

The opportunity to return to academia as a mature student after over 20 years has provided the researcher with a tremendous developmental and learning experience.

Individual impact: The last three years of my PhD have been a deep learning experience. My research in the field of bioethics provided an opportunity to develop critical, analytical thinking and discuss and debate lines of inquiry with likeminded colleagues not only within the university but internationally. The Yale Bioethics summer programme allowed me to fully immerse myself into the historical, philosophical, and theoretical content of bioethics with a practical opportunity to tackle scenarios of ethical dilemmas in the field of research. Furthermore, I have been able to publish some of my work and have been invited to international bioethics conferences to present my work. Last but not least, I have developed excellent networks globally in the field of bioethics.

Institutional Impact: My research study has developed new evidence base on equipoise in a different cultural context. This has a positive impact on my department and the university as such research is rarely being undertaken in LMIC in the arena of Global Health Ethics. My research has also provided my UCL colleagues and the department to foster links with Pakistan with a huge potential for further research studies in the field of bioethics and mental health research.

Impact in LMIC: My research has been based in Pakistan with the Pakistan Institute of Living and Learning (PILL), a not for profit mental health research centre carrying out global mental health research for nearly 21 years. My case study, Youth Culturally adapted Manually Assisted Psychological therapy (YCMAP) is a randomised control trial, which is Medical Research Council funded and is testing this psychological therapy plus treatment as usual versus treatment as usual for Pakistani adolescents who self-harm with a risk of suicide. PILL has kindly funded my PhD. I have been supporting PILL for a number of years on capacity and capability building. As part of my research,
the review of literature on health ethics in Pakistan revealed that bioethics in Pakistan is in its infancy and considerably under developed. In response to my findings, PILL has set up an ethics learning hub with the aim to advance an infrastructure of ethical good practice which is harmonious and responsive to the cultural norms and values of Pakistan. It also serves as a vehicle of cascading learning internally within the organisation as well as externally in Pakistan with an eventual goal of dissemination globally. The Group is chaired by myself with membership of professors in psychiatry, psychology and ethics from Pakistan and the UK, and PILL researchers working towards their PhDs.

**Global Impact:** Already I have presented some of my research at the Global Forum of Bioethics Research and at the 14th World Bioethics Conference in Porto, Portugal. There was a great deal of interest and positive feedback from the international audience. My research will be further disseminated within the university, nationally and internationally. Some of the data which is outside the scope of this thesis requires further research. I would be excited to avail the opportunity to take that forward.
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<tr>
<td>ACT</td>
<td>Adaptive Clinical Trials</td>
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<tr>
<td>BSA</td>
<td>British Sociology Association</td>
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<td>BST</td>
<td>Bio Statistical Theory</td>
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<td>CBT</td>
<td>Cognitive Behaviour Therapy</td>
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<td>CCTU</td>
<td>Cambridge Clinical Trials Unit</td>
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<td>CMAP</td>
<td>Culturally adapted Manually Assisted brief Psychological intervention</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<tr>
<td>CRPD</td>
<td>Convention on the Rights of Persons with Disabilities</td>
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<td>DALY</td>
<td>Disability Adjusted Life Years</td>
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<td>EBM</td>
<td>Evidence Based Medicine</td>
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<td>EBR</td>
<td>Evidence Based Research</td>
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<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
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<td>EMBRO</td>
<td>European Office for the Eastern Mediterranean</td>
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<tr>
<td>ERC</td>
<td>Ethics Review Committee</td>
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<td>FDA</td>
<td>Food and Drug administration Agency</td>
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<td>FGD</td>
<td>Focus Group Discussion</td>
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<td>FRA</td>
<td>Fixed Randomisation Allocation</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>HCEC</td>
<td>HealthCare Ethics Committee</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HIC</td>
<td>High Income Countries</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
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<tr>
<td>IHC</td>
<td>International Council for Harmonisation</td>
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<tr>
<td>IR</td>
<td>Implementation Research</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>JBI</td>
<td>Joanna Briggs Institute</td>
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<tr>
<td>LMIC</td>
<td>Lower- and Middle-Income Countries</td>
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<tr>
<td>MedCOI</td>
<td>European Commission Medical Country of Origin</td>
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<tr>
<td>MNA</td>
<td>Member of the National Assembly</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>MTCT</td>
<td>Mother To Child Transmission</td>
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<td>NBC</td>
<td>National Bioethics Committee</td>
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<td>NGO</td>
<td>Non-Governmental Organisation</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
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<td>NIHR</td>
<td>National Institute of Health Research</td>
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<tr>
<td>OECD</td>
<td>Organisation of Economic Co-operation and Development</td>
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<tr>
<td>OHCHR</td>
<td>Office of High Commission of Human Rights</td>
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<tr>
<td>OPD</td>
<td>Out Patient Department</td>
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<tr>
<td>PBH</td>
<td>Peace Be upon Him</td>
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<tr>
<td>PILL</td>
<td>Pakistan Institute of Living and Learning</td>
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<tr>
<td>PKD</td>
<td>Polycystic Kidney Disease</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>PMDC</td>
<td>Pakistan Medical and Dental Council</td>
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<td>PPIE</td>
<td>Public and Patient Involvement and Engagement</td>
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<td>PROMS</td>
<td>Patient Reported Outcome Measures</td>
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<td>QALY</td>
<td>Quality Adjusted Life Years</td>
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<tr>
<td>RAR</td>
<td>Response Adaptive Randomisation</td>
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<td>RCT</td>
<td>Randomised Clinical Trial</td>
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<td>REC</td>
<td>Review Ethics Committees</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>SDGs</td>
<td>Sustainable Development Goals</td>
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<tr>
<td>SR</td>
<td>Systematic Review</td>
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<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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<td>STS</td>
<td>Science and Technology Studies</td>
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<tr>
<td>TAU</td>
<td>Treatment As Usual</td>
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<td>TM</td>
<td>Therapeutic Misconception</td>
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<td>UCL</td>
<td>University College London</td>
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<td>UHC</td>
<td>Universal Health Coverage</td>
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<td>UN</td>
<td>United Nations</td>
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<td>UNCRC</td>
<td>United Nations Convention of Rights of the Child</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<td>YCMAP</td>
<td>Youth Culturally adapted Manually Assisted Psychological intervention</td>
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1.1 Introduction

There has been increasing academic and policy interest in the ethics of research over the past few decades. Particular issues that have been neglected relate to ethics of evidence and clinical trials, although attention has largely been focussed on consent (Edwards et al., 1999); questions over the role of other moral requirements such as equipoise and risk still remain.

Over 30 years ago Benjamin Freedman introduced the concept of equipoise;

“It is uncertainty or equal belief that there is equal balance between the two treatments in the trial and that one is equally effective than the other” (Freedman, 1987)

Also, according to London (2017), “The principle of equipoise states that, when there is uncertainty or conflicting expert opinion about the relative merits of diagnostic, prevention, or treatment options, allocating interventions to individuals in a manner that allows the generation of new knowledge (e.g. randomisation) is ethically permissible”. This concept served as a foundation of research ethics. However, more recently, there is resurgence of interest and debate on the concept of equipoise especially with the rise of innovative trial designs (Hey et al., 2017). In particular, there is difference of opinion over relevance and importance of individual level uncertainty over evidence, as opposed to professional or ‘collective’ level epistemic uncertainty (Weijer et al., 2001). Lilford et al, argue Freedman’s concept of clinical equipoise is discordant with individual patients’ autonomy and choices where different people may hold different value systems and decision on participating in clinical trials may have very different trade offs

One criticism of the concept of individual equipoise is that it is very fragile. Any new data would be enough to knock the individual clinician out of state of uncertainty, if indeed she were ever in that state. These data may or may not
serve as sufficient evidence to persuade clinicians to adopt the trial results and to influence standard of care or policy. It is not clear how much data should comprise enough evidence of relative efficacy, or why practitioners fail to adopt results when scientists judge them to be definitive. Also, why practitioners at times adopt technologies with little evidence.

The existence of equipoise does not necessarily lead to important research. Public health and policy interventions are progressively evaluated, because it is increasingly agreed that public health research has not delivered credible evidence as often as it could have. We should also consider the ethics of not doing research. If less than 10% of current global funding for research goes to diseases that afflict more than 90% of the population (the “10/90 gap”) (Vidyasagar, 2006), this gap is itself an ethical issue. Good research tells us if things work – or if they don’t – and ethics may be served equally by protecting people from exposure to costly and ineffective interventions. (Osirin et al., 2009)

The debate on the ethics of international clinical research involving collaboration with Low and Middle Income Countries (LMIC) is of considerable significance because of increased interest in global health research (Benatar, 2001). This makes it an imperative that research is equitable, just, relevant to the context in which it is organised and responsive to local health needs. Global health ethics is emerging as a new discipline (Benatar, 2002; Marshall, 2006). Although the field of global health ethics is largely underpinned by the concepts of bioethics from High Income Countries (HIC), the decolonising global health agenda acknowledges that it is increasingly important to examine such concepts in different cultural and social contexts. Concerning ethics, Bernal and Adames (2017) stated that “we caution to impose views, norms and values of the world’s dominant HIC society onto vulnerable populations such as ethno-cultural groups”. Considered in the round, the discipline of research ethics is mostly ‘Euro-American’ and not often recognised, let alone adapted for, within many other cultures (Zaman and Nahar, 2011; Stepleton et al, 2014). For example, Zaman and Nahar note that
when conducting research in Bangladesh, they found the word ‘research’ did not exist in the Bengali language and when translated meant ‘finding a lost cow’. Global health projects have too often been developed without the input of LMIC local partners, leading to claims of neo-colonialism (Provenzano, 2010). The conditional adherence to HIC governance models by the funders of research who are predominantly from the global north could similarly be seen as neo-colonial.

In defining “Global Health Ethics” Myers (2015) likewise observed “that existing literature on global health ethics has majorly originated from North American medical doctors. According to Laurence and Hirsch, 2020, in global health research there exists a power imbalance between researchers from HIC and LMIC researchers and state that these inequalities largely stem from colonialism. Prompted by the decolonising global health movement. I, the researcher conducted a random search of literature using the terms ‘community engagement’, ‘global health ethics’, ‘global health research and ‘global health partnerships’ from 2016 to 2020, which revealed around 102 articles mostly from HIC. This was inferred from the first author’s names. My search corroborated with the above observations. Therefore, the question of whose perspectives, views, plans as well as advances, the global health ethics actually represents and how and why – invites scrutiny” (Myers, 2015). As Japanese historian William LeFleur once commented, “though bioethics has become international, it has not become ‘internationalised” (Fox RC and Swazy, J P, 2010). HIC principles of bioethics focus on the individual’s rights of autonomy and consent disregarding the collectivistic cultural norms of interconnectedness of role of the family and how shared decision making is intertwined in some cultures. Consequently, despite all good intentions towards research participants, researchers possess a certain ‘ethnocentrism’ before research begins. While research carried out in a respectful manner has maximised social value (Molyneux and Bull, 2013), community engagement or community consultation in the proposed research projects has emerged as a requirement for ethical international research (Provenzano, 2010). It refers to
participation and involvement of people, groups, structures or community members for planning, design, decision-making, and governance to promote people centred delivery of services (Barker et al., 2020). Community engagement has recently been seen as critical and fundamental component of many health initiatives, particularly during disease outbreaks (Kuruvilla et al., 2016). This entails understanding of the emergent global health gaps and of the lifestyle of potential research participants. In their book, Understanding Global Health, Velji and Bryant (2007) state that when conducting research, global health ethics not only challenge their practitioners to identify potential research subjects but to assure respect for justice, dignity and human rights. It is necessary to understand the different mind sets, environments and frameworks of thinking while undertaking collaborative research in LMIC (Benatar, 2002). Odugleh-Kolev and Sprowl (2019) emphasised the importance of addressing those aspects of health systems that continue to hinder efforts to meaningfully engage with patients, their families and local communities. In today’s world, when researchers may not reside in the communities where they work, knowing their experiences and culture i.e. differences in political, cultural and social structures, systems and processes among communities, social norms and beliefs is important.

With the World Health Organisation (WHO) global health agenda (2020) and the UN Sustainable Development Goals (SDG’s) of 2030 (2015) more and more young researchers want to apply their skills to global health research. It is a good thing that more and more research is being carried out in the pursuit of global health and that researchers and institutions from HIC are invited to build research capacity and capability. As part of these projects, researchers from HIC are often involved in community engagement workshops. In culturally diverse environments where linguistic and cultural barriers exist, standards for effective communication might be daunting (Benatar, 2002; Mrshall, 2006). Researchers from HIC are often unsure of the cultural norms, values and beliefs of local communities. Consequently, they may sometimes unknowingly come across as insensitive and disrespectful. “How do we begin
to think about unintended consequences when we are doing what we presume as ‘good’ for the patient, for their family, the community and society at large” (Kuruvilla et al., 2016).

Implementation of health research requires understanding and engaging key stakeholders at all levels of the local health systems. Cultural and linguistic variances, historic legacy of mistrust, manipulation within the research enterprise and scientific colonisation concerns further intensify these conditions (King et al 2014). MacLachlan (2010) highlighted how communities may see foreign aid workers as symbols of colonialism, capitalism, and eurocentrism. Conversely, communities may perceive the doctor from HIC to have magical powers and superior expertise. This can give rise to unrealistic expectations. To counter this, honesty must be a universal commitment (Kuruvilla et al., 2016). Motivated by the decolonising global health agenda, this thesis has also provided the researcher an opportunity to add her voice towards global health becoming more inclusive and just.

1.2 The Research Question

The overall aim of this thesis is to examine the main concepts of equipoise and apply them in a different cultural context.

The main focus of my research is whether the clinicians recruiting patients in the cultural context of Pakistan have a personal preference for one or other treatment. If they do have a preference, I wanted to find out which they favour, and whether they regard participation in a Randomised Clinical Trial (RCT) as scientifically and ethically important and necessary despite these personal preferences?

My specific research questions are:

(i) Which intervention is preferable to the clinicians? YCMAP plus TAU compared to TAU only for young patients at risk of self-harm and suicide, as measured by the responses of clinicians both involved in the trial and those not involved in the trial?
(ii) Whether there is uncertainty in clinicians to justify conducting Randomised Clinical Trial?

(iii) What are the potential cultural, moral and religious barriers and potential ethical issues needed to be considered when planning RCTs in Pakistan?

(iv) What will be needed to persuade policy makers and funders, health professionals and participants to adopt psychological therapies to become standard care for young people who self-harm in Pakistan?

1.3 Study Design

The methods that I, the researcher have used include both, qualitative and quantitative approaches to investigate how cultural, moral and religious values relate to western concepts of research ethics? Inductive analysis of the normative questions around the moral justification of multi centred randomised clinical trials such as YCMAP as well as an empirical study of the views and values of practitioners and members of policy bodies. The latter includes members of the ministry of health and clinicians. The rationale to gathering policy makers' views was to gauge how much evidence they would require to persuade them to adopt the psychological interventions as standard care. I used the following methods to gather data:

- Survey of clinicians, those recruiting patients to YCMAP and those not involved in the trial.
- Cultural inquiry through focus group with researchers.
- Semi structured interviews with clinicians, those recruiting patients to YCMAP and those not involved in the trial.
- Conversations with government policy makers in Pakistan.
**Research Aim:** The overall aim of this thesis is to examine the main concepts of equipoise and apply them in the cultural context of Pakistan.

**Chapter 2:** Background: Introduces the key concepts of equipoise underpinning this PhD and offers a critique of the literature

**Chapter 3:** Pakistan Context: Describes the case study predicated on an exploratory review of health and research ethics in Pakistan in order to gain an understanding of the current situation of bioethics and the challenges of utilising western bioethical principles in a different cultural, social and religious context, exploring Islamic approaches to research ethics and finally leading to a discourse on the ethical considerations regarding clinical trials and human rights law.

**Methodologies:** A mixed approach of data collection using interdisciplinary methods.

**Chapter 4:** Quantitative Research: A cross sectional survey of clinicians

**Chapter 5:** Qualitative Research
1) Focus group discussion with researchers to investigate the cultural context of Pakistan
2) Semi structured interviews with the clinicians, both involved in the trial and those not involved in the trial to contextualise the western conceptions of equipoise
3) Conversations with policy makers to assess whether they had an understanding of mental health issues in Pakistan and what would convince them to promote psychological interventions as standard of care for prevention of self-harm and suicide in adolescents

**Chapter 6:** Discussion

**Chapter 7:** Conclusions

**Chapter 8:** Recommendations

Figure 1: Thesis Outline - Connection between the Four Research Questions and the Research Design, and different aspects of the
Chapter 2: Background

This section examines the broader literature concerning equipoise.

According to Lilford et al (2001), the need to generate new knowledge for the benefit of society at large is aligned to patients’ best interest. However, what is best interest is dependent very much on an individual’s own value system. Lilford (2001) suggest that if we hold autonomy as a fundamental ethical principle, patient equipoise should be regarded as equally important and justifiable. It is also reported patient centred clinical trials produce better outcomes even when there are null results (Lilford, 2001). Hence, Lilford’s suggestion of a contemporary shared decision-making model of community equipoise. Based on this perspective, the burden of ethical justification is equally divided between patient equipoise and clinical equipoise (Hey and Trough, 2015). On these grounds, I proceed to discuss the importance of safeguarding rights of human subjects in medical research and advance the discussion on human rights law and rights to health of human subjects as participants in RCTs.

As my research case study is based in Pakistan, I did an exploratory literature review in order to gain an insight into the current status of health ethics in Pakistan. Also, as 95% of the population of Pakistan is predominantly Muslim, I have attempted to review the limited literature available (mostly from the Middle East) on Islamic approaches to research ethics in order to gain an understanding of the religious and cultural context of medical research and research ethics. Finally, through discussion group with Pakistani researchers, I have identified key themes to inform the development of a community engagement tool for western researchers. This initial work has demonstrated the differences in religious and cultural beliefs and values. Given these differences, my project seeks to further critically investigate the cultural context through my qualitative research in order to contextualise the western concepts of equipoise.
2.1 Research ethics theory – concept of equipoise

To start with, my thesis sets out the conceptual and theoretical background of equipoise as well as analyse, clarify and examine the importance of equipoise as an ethical prerequisite to carrying out RCTs. This segment will first discuss the concept of equipoise and different forms of the constructs such as absolute, individual, and clinical equipoise. Secondly, according to Benjamin Freedman clinical equipoise is favoured to be the most robust (Freedman, 1987), accordingly it will present the discourse on the alternatives to the concept of clinical equipoise by doing an analysis of the challenges and debate on clinical equipoise, as an overall concept for moral justification for conducting RCTs.

It is widely believed that randomisation provides the best evidence base for clinical care and would be of advantage to the participants (Lilford and Jackson, 1995). Equipoise as an ethical framework looks at whether there is any treatment preference between interventions and if there is a preference, is it by the collective of clinicians, individual clinicians, or participants/patients? We do not know until the end of the trial which treatment is better so we are relying on prior beliefs of clinician/researchers. These may be based on smaller trials, past mistakes from the history of medicine or from evidence from animal trial or a different set of populations and contexts.

2.1.1 The Concept of Equipoise

In 1974, Charles Fried developed the moral justification of conducting RCTs which he termed as Equipoise. According to Fried “if an individual physician does not have any preference to the trial interventions and is equally uncertain about the benefits for her patients, she is ethically justified in recruiting her patients in the RCT.” (Charles Fried, 1974)

Freedman (1987) stated that it is uncertainty or equal belief that there is equal balance between the two treatments in the trial and that one is equally effective as the other. Freedman referred to ‘individual’ equipoise which was
when an individual clinician was uncertain, or ‘expert’ equipoise when a community of clinicians was uncertain. This is termed as ‘clinical equipoise’ and believed to be the most robust ethical principle for conducting medical research and randomisation (Lilford and Jackson, 1995).

While the above broadly describes the concept of equipoise, there are other theories of equipoise which require discourse.

2.1.2 Absolute Equipoise

Equipoise is a state of mind where the degree of justifiable uncertainty about the truth value of a particular preposition is balanced to some extent (Ashcroft, 1999; Lilford, 2001).

The discussion now moves on to not just whether one treatment is better than the other, but as most treatments have more than one effect, the participants' perception of the values of different effects plays a part in the decision-making process. Lilford and Jackson (1995) define where treatment options have the same effect as ‘absolute’ equipoise. It may seem that in some clinical trials the participants may not reap the benefit or may even be at risk of harm, but based on the principle of non-maleficence, it is morally justified to conduct a clinical trial when many more people stand to benefit than not in such clinical trials.

2.1.3 Individual Equipoise

“The ethics of clinical research requires equipoise — a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial” (Freedman, 1987, pg1).

In 1974, Charles Fried developed the concept of individual or theoretical equipoise which set the social standard for conducting RCTs. Fried’s approach suggested that if an individual clinician does not have any preference for the trial interventions, and is equally uncertain about the
benefits for her patients, she is then ethically justified in recruiting her patients to the RCT. However, Benjamin Freedman in 1987 declared individual equipoise to be ‘flawed’. This is on the basis that an individual clinicians’ preference may be founded on intuitive or other biases such as their clinical attitudes, prior experience and their own interpretation of available literature. Freedman suggests that even though an individual clinician would regard one treatment to be better than the other, if there is collective equipoise then they would be ethically justified to offer patient entry in the trial. He goes on to concur that clinicians even when in individual equipoise should follow the principle of adherence to the collective norms to avoid the inherent risk of bias.

Individual clinician/investigator equipoise also brings into question the two concepts of doctor/patient trust relationship and duty of care towards the individual patient. Literature suggests that the doctor/patient relationship of trust often relies on this trust based obligation of the clinician and that she will act in the best interest of her patient. The trust-based obligations of a clinician for her patient is underpinned by the bioethical principle of beneficence. An individual clinician’s perception of there being a risk to maintain patient/doctor trust could conceivably be a source of tension between individual clinician opinion and collective/expert equipoise. In the interest of patient/doctor relationship, it will be an ethical imperative for the individual doctor to declare their preference to the patient, at the time of gaining consent when recruiting the patient into the trial.

The aim of clinical research is to generate scientific knowledge for the benefit of public interest and welfare. Participation in research by volunteer patients makes this possible (Miller and Weijer, 2007). The patient’s decision to participate in research is a trust relationship based on the premise that research bodies at large are set up by the state to protect the interest of patients as research subjects. In return the patients, by participating in research will contribute to scientific knowledge development and for the good of the whole society.
All approaches of equipoise are fundamentally underpinned by the principle of ‘do no harm’ and ‘duty of care’ to the patient (participant) and to be clinically in the best interest of the patient. This independent responsibility of ‘duty of care’ protects the agent-relative welfare (the unequivocal doctor/patient relationship) of the patient as participant. Equipoise ensures that treatment arms of an RCT are balanced and consistent with competent medical care. On the other hand, research is primarily in the pursuit of knowledge and for scientific advancement in the interest of the public. Here, the quandary arises that recruiting a patient subject in an RCT, a clinicians’ duty to act in the interest of their patient could be jeopardised, as the RCT aims to produce wider knowledge in the public interest and other variables such as private industry, researchers, and other interests also come into play.

Due to the above conflict, in the view of Hellman and Hellman (1991), RCTs actually violate the rights of patient subjects and they concur that RCTs should only be carried out on non-human subjects. According to Miller and Weijer (2007), this is considered a flawed view as RCTs have, for generations played a major role in the advancement of knowledge and science.

Miller et al. (2003) argue that the role of the doctor-clinician and of the doctor-researcher have two different purposes, suggesting that the doctor-researcher in the enrolment of a patient-subject, in a randomised clinical trial is primarily acting in the interest of the public. This moral dissociation is problematic and is in tension with the doctor-clinician trust-based obligation, to act in the interest of their patient.

Individual equipoise could be problematic due to its ‘fragile epistemic threshold’ as it has the potential of tipping the balance of preference towards one or the other intervention as discussed before. Nonetheless, it could be argued that participants in trials, do in general benefit. Even if they end up in the inferior arm of the trial, the close monitoring and overall attention by rigorously following protocols of the trial would give psychological boost to the participant (Lilford and Jackson1995). Hence, a clinician’s duty to offer entry
to patient in a trial is justified where the patient may receive the treatment through randomisation which otherwise, may not be available to them due to lack of resources.

2.1.4 Clinical Equipoise

Freedman suggests an alternative concept of equipoise which offers a more robust epistemic threshold, which would be based on controversy and uncertainty in the clinical community over the preferred treatment. This concept he called clinical equipoise, where the requirement is satisfied if there is genuine uncertainty within the expert medical community about the preferred treatment (Freedman, 1987).

The scientific rationale based on Freedman's concept of equipoise is ‘clinical equipoise’. When there is no consensus amongst the expert medical community on the merits of different medical interventions, then it is ethically and morally justified to conduct RCTs (Miller, 2012). The scientific expert community continues to endorse clinical equipoise as the most rigorous and ethical basis for undertaking RCTs based on the rationale that the collective uncertainty counterbalances the fragility of individual equipoise.

The ethical discourse on the relevance of clinical equipoise continues. It is interesting to note from Katz et al. (2010) study that there is a marked divergence from the efficacy of a RCT, when participant recruitment is based on ‘individual equipoise’ and where a clinicians’ selection enrolment is based on their own clinical preference. The study showed that there was more accuracy of trial results where ‘clinical equipoise’ exists. (Katz et al., 2010). The study discovered that selective enrolment disregarded the inclusion/exclusion criteria of the trial and introduced other clinically preferred factors of the clinician researcher. Population based selection purely grounded upon randomisation (clinical equipoise) resulted in more accurate trial results on the efficacy of the treatment.
Challenges to the concept of clinical equipoise

De Meulemeester et al. (2018), in their cross-sectional analysis of published literature on RCTs conclude that equipoise, although widely accepted as a scientific criteria and moral justification for conducting trials, rarely appeared in published literature. Furthermore, it appeared inconsistently and was often misunderstood. A similar picture has emerged within my research. De Meulemeester et al. (2018), argue that the utility of the concept of clinical equipoise as an ethical standard for justification of RCTs should be challenged.

There is also criticism and strong opinions amongst experts on the ethics of randomisation and of the influence of funders and motives of investigators on the trial. Some critics arguing the requirement of clinical equipoise in randomisation as defective and furthermore, failure of clinician investigator of using their judgment in the best interest of the patient. (Miller and Brody 2007). This debate goes on; but for now, RCTs remain the best way to reach robust conclusions about the comparative value of medical treatments. Thus, we must continue conducting clinical trials (Rabinstein et al., 2018).

The doctor/clinician and the doctor/researcher dilemma

In a clinical setting the obligation of the doctor is to act in the best interest of her patient. On the other hand, the doctor as the researcher is recruiting the participant research for the purpose of research, in the pursuit of new knowledge and for the good of society as a whole. “A predominant ethical view holds that physician-investigators should conduct therapeutic intent. And since a physician offering a therapy wouldn't prescribe second rate treatments, the experimental intervention and the best-proven therapy should appear equally effective. “Clinical equipoise” is necessary. But this perspective is flawed. The ethics of research and of therapy are fundamentally different, and clinical equipoise should be abandoned” (Miller and Brody 2003). This suggests that clinical practice and clinical research are two different things, medical therapy being more concerned with finding the
optimum treatment for the patient, while the primary aim of clinical research is to ‘increase knowledge’. Miller and Brody (2007) go on to state that “some critics arguing the requirement of clinical equipoise in randomisation as defective and moreover, failure of clinician investigator to use their judgment in the best interest of the patient”. Miller and colleagues maintain that clinical research and therapeutic practice are two different activities. However, bioethicists and clinical investigators would question the moral conflict of this statement with the ‘duty of care’ and ‘do no harm’ obligations of the doctor towards her patients.

Van der Graaf and Van Delden (2011) concur that there is a lot of overlap between the proponents and opponents of equipoise as defined by Freedman (1987). They go on to discuss Chiong’s (2006) point of view that ‘physicians in the research context do have a role related obligation but these obligations do not require physicians (to promote) the best medical interest of the patient’. Chiong’s reasoning is based on the utilitarian view advocating the moral societal centred stance that less than optimal care to some patients is justified by the potential benefit of others in the study. Gifford (2007) although not denying the deontological patient centred obligations of the physician researcher role, joins league that ‘equipoise does not prevent that the therapeutic obligation is sometimes violated in clinical research’.

According to Van der Graaf and Van Delden (2011), Choing (2006) and Gifford (2007) may have given up on clinical equipoise but Miller and Weijer (2007) continue to favour the concept on the basis that equipoise is underpinned by the bioethical principles of beneficence and non-maleficence. Nevertheless, Miller and Weijer (2007) reject individual equipoise due to its fragile threshold in favour of clinical equipoise.

**Barrier of inherent treatment preference**

A major challenging area for inherent bias is surgical trials. Normally, new inventions of surgical procedures are by an individual surgeon or a group of surgeons. The enthusiasm of the surgeon/surgeons towards their invention
intuitively lends itself to favouring the new procedure. This would deem to disrupt clinical equipoise. Furthermore, the process of blinding in the case of surgical procedures is problematic, as the surgeon herself will be performing the procedure. Due to lack of clinical equipoise, which is the ethical grounding for conducting RCTs, there appear to be fewer RCTs conducted and published in surgical fields (Campbell et al., 2009). Clinical equipoise is an essential ethical imperative for RCTs. However, in the case of surgical RCTs, the deficit of rigorous scientific data and evidence base of high quality RCTs often result in surgeons depending on uncorroborated data. (Campbell et al, 2009). The underlying bias and lack of rigorous data is hugely problematic as it potentially alters and disrupts clinical equipoise.

**Accumulation of data disrupts clinical equipoise**

Halpern argues that in medical matters, the presence of equipoise should be based on evidence and not on expert consensus opinion (Halpern, 2006).

Deng et al. (2012) propose that where there may be a lack of clinical equipoise particularly in placebo-controlled phase 3 trials, regulatory bodies should look at more innovative trial designs to cope with the problem of accumulating data disrupting equipoise. Deng et al go on to question, whether clinical equipoise could ever exist in Phase 3 large scale trials. The challenge here is also the accumulation of data at this late stage of trial development, where there is already animal data, data from uncontrolled RCTs and evidence from other similar trials. The accumulation of data during an RCT would be problematic, as it could also challenge the existence of clinical equipoise. However, normally the data is not shared with investigators until the end of the trial period. Any modification or stoppage, if required, is the responsibility of the monitoring committee during the accumulation of the data. However, if the emerging data of a trial shows benefits of the new treatment, this can be problematic as there is a tendency for the data monitoring committees to terminate the trial and based on this, health policy decisions are made prematurely. This doesn’t only disrupt clinical equipoise but could
also be detrimental in the long run, both from the lack of rigorous evidence on adverse treatment effects as well as efficacy of the new treatment (Deng et al., 2012).

Deng et al (2012) suggest that where clinical equipoise is in question, the onus should lie with the regulatory authorities and drug manufacturers (in case of drug trials) to provide appropriate evidence to the regulators, thus taking the ethical obligation away from the clinician and protecting the patient. The legal and moral duties of the state make it incumbent on the national research organisations to abide by the rules and regulations set out to protect the patient and public interest. The ethical obligation of both clinicians and ethics committees is to safeguard individual rights of patients and hence act in their best interest, as well as to propagate research, in the interest of society (Miller and Weijer, 2007). Clinical equipoise ensures treatment arms of a RCT are balanced and consistent with competent medical care. At the point of enrolment, the clinician-researcher will use the ‘principle of clinical judgement’ (Miller and Weijer, 2006) in the best interest of the patient and their circumstances. The Review Ethics Committees (REC) role is to ensure that protocols meet the ethical and scientific standards. Additionally, a major role of the REC is to establish that the trial will meet the bioethical principles of beneficence and non-maleficence i.e. the study will do no harm to the patient subjects, will add value to the scientific knowledge and will benefit the public at large. The ethics committee needs to be in collective equipoise, to give ethics approval to a trial. The perception of a trial having gained ethics approval by a committee of experts also gives confidence to the participants that the trial is in their best interest.

Practical Challenges

Roosshenas et al. (2016) state that “much of the literature around clinical equipoise has been theoretical, although there have been some empirical studies, that have focused on clinicians’ reported difficulties with negotiating equipoise. These studies indicate that clinicians often assume that personal
struggles with equipoise, can be set aside during patient encounters and have no bearing on recruitment”.

In the context of clinical investigators recruiting participants in trials, there are three main themes occurring:

a) Fragility: There is concern about the fragile epistemic threshold, due to clinicians’ communication skills on their individual equipoise and their own perception of the impact on recruitment. Rooshenas et al. (2016) conclude that when the patient is uncertain, the clinician may declare their perceptions and share their own preference thus disrupting equipoise. Donovan et al. (2014) in their study, argue that sub optimum recruitment into trials make the validity of the RCTs fragile. The impact of this fragility results in the waste of scarce resources and begs the question of overall effectiveness of RCTs. Generally, doctors are motivated to participate in RCTs for the sake of advancement of scientific knowledge and evidence base. However, often there is a tension between what is required of the RCT and their own intuitions for the benefit of their patients, with regards to suitability and safety for enrolment in the trial. Consequently, although the doctors are comfortable with the concept of clinical equipoise as a general ethical framework for conducting RCTs, it becomes problematic for them when they are recruiting their own patients into a particular RCT (Donovan et al., 2014). This intellectual tension and emotional struggle have a detrimental impact on the recruitment process.

b) Impact of Speciality: It is also interesting to note that the application of equipoise varies from speciality to speciality. For example, Donovan et al. (2014) in their study reported that surgeons would intuitively believe that surgery would be the best treatment option. There is uncertainty around the point of ‘no treatment effect’ and uncertainty around the point where patient has no preference as ‘effective’ equipoise. This is also where patient trade off value corresponds with the clinicians most likely treatment effect e.g., breast mutation versus prolonging of life.
This bias was linked to the speciality they chose to work in. Individual doctors’ biases, hunches and intuitions are problematic and add to the fragility of the recruitment process. Lilford and Jackson conclude that patient interest and advancement of science necessitates clinical trials. The discourse on the continued use of clinical equipoise as the best legal and ethical justification has resulted in polarised views amongst scholars, some fervently favouring clinical equipoise while others debate on the demise of it. There is even the suggestion by some that recruitment to RCTs should be done by nurses and other research staff, on the rationale that they would remain more neutral, as they do not have the clinical decision-making responsibility (Donovan et al., 2003).

c) Gap in doctors’ training and communication skills: This remains a major issue contributing to difficulties in poor recruitment in RCTs. The notion that the clinician would be so uncertain about the benefits of each treatment in the RCT, and that their doctor will not be assigning them to the ‘better treatment’ in the trial is hard for patients to fathom. More so, as they believe that their doctor, knowing their medical history and records, would allocate the best treatment intervention for their patient. Even if patients accept that there could be ‘uncertainty’, they remain less comfortable with medical uncertainty compared to non-medical uncertainty. Even though, the RCT is explained to the patients, there remains a significant amount of misconception on the part of the patients that participating in the trial means that they will get the best treatment. (Campbell et al., 2009). One of the barriers is also that, in many cases most researchers find it easier to explain the straightforward parts of the RCTs rather than the complex areas. This is quite concerning and raises the question as to; how ‘informed’ is informed consent. The whole issue becomes even more problematic in the case of children where parents would be more reluctant to consent, on the basis that their child may randomly be assigned to a treatment that may not be of benefit to the child. Another barrier is also the
retention of participants, and the reasons are multi-factorial. These could be the length of the study, move to another area etc.

**Net Risk Approach – An alternative to Equipoise**

As the controversy and debate continues Rid and Miller (2017) state that “many clinical trials include procedures with some level of “net risk” to participants, meaning that the procedures are done purely for research purposes and hence do not promote participants’ best clinical interests”. They propose ‘Net Risk’ as an alternative to the concept of clinical equipoise.

The Belmont Report (1979) mandated a system of risk-benefit analysis for proposed research on human subjects. Hence, RECs should conduct risk-benefit assessments on trials proposed to be carried out on human subjects. These are to ensure that participants are protected and not exposed to unnecessary risks. Charles Weijer and Paul Miller developed a procedure level approach which begins with assessing the therapeutic component of the protocol with the existence of clinical equipoise.

In response to Weijer and Miller's Component Analysis decision tree, David Wendler and Franklin Miller developed the Net Risk Test. This procedure-level approach requires firstly an analysis of minimising risks of all interventions in the study and then evaluation of the clinical risk-benefit of the intervention. If the potential clinical benefit outweighs the risks, then the intervention should be acceptable to the REC the corollary being that the net risk i.e., risk of harm is low enough to justify the social value of the intervention. Finally, the cumulative net risk of all interventions in the study is calculated to make certain that the cumulative sum of risk does not outweigh the potential benefits. This Net Risk Approach has been further refined into a seven step Framework by Rid and Wendler. These two procedure level approaches have some similarities, but a fundamental difference is that Wendler and Miller disregard the requirement of equipoise within their approach.
Miller and Joffe (2015) argue the merits of clinical equipoise as a sole focus on which to justify conducting RCTs but raise a pertinent point of cost-effectiveness, to be a principle also to be considered. In the face of advancement in medical science and the high cost of medical devices and technology, they propose the evaluation of the net clinical benefits arguing that access to new treatment with marginal net benefit clinically does not justify the high cost. Also, in the case of trials for treatment of rare diseases, as long as the participants are not harmed, disruption of equipoise is ethically a must in the interest of the patient population as a whole (Miller and Joffe, 2015)

In summary, after its inception, equipoise became rapidly embraced as a necessary condition for randomisation in clinical trials. However, the conceptual controversies and practical application of this ethical framework has proven far from straightforward. (Rabinstien et al., 2018). There is continued debate on the relevance of equipoise as ethical and moral justification for randomisation. Some scientists arguing that with the advent of innovative trial designs, the concept of equipoise is outdated. On analysis, all approaches of equipoise are fundamentally underpinned by the principles of ‘do no harm’ and ‘duty of care’ to the patient (participant) and to be clinically in the best interest of the patient. However, on the other side of the debate, there is even a suggestion to consider ‘net risk’ as an alternative approach to the concept of equipoise as an ethical framework for conducting RCTs. Rid and Miller (2017) proposed net risk as an alternative approach that “clinical investigators do not have the same obligations to promote the participants clinical interest to generate “clinically valuable knowledge”. This seems to oppose the basic ethical principles of beneficence and non-maleficence. The ‘net risk’ approach used by RECs as part of the process of ethical justification is fine however, Weijer and Miller’s approach predicated on ‘clinical equipoise’ provides greater protection to the research participants. Also, from the participant benefit point of view, Lilford and Jackson (1995) stated that even participants in the inferior arm of the trial get a psychological boost by
continued monitoring and the rigour of the trial protocols. In the era of patient centred ness, the lack of communication skills of researchers and providers is problematic from the point of view of patients fully understanding the risks. A focus on training is required both for the clinicians and research staff as well as for the patients. Elliot et al (2018) also concluded that better training will help recruiters to better explain equipoise and convey information fully to the patients. This would ensure patients properly understand and are able to give independent consent or decide to decline taking part in the RCT. Better trained doctors and researchers would be more confident and competent in providing neutral information to patients at the time of recruitment, thus maintaining clinical equipoise and without suggesting which randomisation allocation would be more efficient, in which trial design and when.
Table 1: Clinician reported difficulties negotiating with equipoise

<table>
<thead>
<tr>
<th>Author</th>
<th>Main Results</th>
<th>Theme</th>
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<tr>
<td>Rooshenas et al, 2016</td>
<td>When the patient is uncertain, the clinician may declare their perceptions and share their own preference thus disrupting equipoise. Sub optimum recruitment into trials make the validity of the RCTs fragile. Although the doctors are comfortable with the concept of clinical equipoise as a general ethical framework for conducting RCTs, it becomes problematic for them when they are recruiting their own patients into a particular RCT.</td>
<td>Fragility</td>
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<tr>
<td>Donovan et al, 2014</td>
<td>Application of equipoise varies from speciality to speciality. For example, surgeons would intuitively believe that surgery would be the best treatment option.</td>
<td>Impact of speciality</td>
</tr>
<tr>
<td>Campbell et al, 2009</td>
<td>In many cases most clinicians as researchers find it easier to explain the straightforward parts of the RCTs rather than the complex areas. This is quite concerning and raises the question as to; how ‘informed’ is informed consent.</td>
<td>Gap in doctors training and communication skills</td>
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Below is the quality assessment of the qualitative studies, texts and opinion papers using Joanna Briggs Institute quality assessment tools:
Table 1a: Checklist for quality assessment of qualitative studies

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<thead>
<tr>
<th>Author and Year</th>
<th>Donovan et al. (2014)</th>
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<td><strong>Comments:</strong> (Yes, No, Unclear, Not applicable)</td>
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</table>

1. Is there congruity between the stated /theoretical perspective/rationale and the research methodology? **Yes**

2. Is there congruity between the research methodology and the research question or objectives? **Yes**

3. Is there congruity between the research methodology and the methods used to collect data? **Yes**

4. Is there congruity between the research methodology and the representation and analysis of data? **Yes**

5. Is there congruity between the research methodology and the interpretation of results? **Yes**

6. Is there a statement locating the researcher culturally or theoretically? **Not applicable**

7. Is the influence of the researcher on the research, and vice-versa, addressed? **No**

8. Are participants, and their voices, adequately represented? **Yes**

9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body? **Yes**

10. Does the conclusions drawn in the research report flow from the analysis, or interpretation, of the data? **Yes**

**Overall Quality:**
Low/Moderate/High **High**
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Rooshenas et al. (2016)</th>
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<tr>
<td><strong>Comments:</strong> (Yes, No, Unclear, Not applicable)</td>
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<tr>
<td>1. Is there congruity between the stated /theoretical perspective/rationale and the research methodology?</td>
<td>Yes, research methodology was appropriate.</td>
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<tr>
<td>2. Is there congruity between the research methodology and the research question or objectives?</td>
<td>Yes, the research methodology was in line with the study objective.</td>
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<td>3. Is there congruity between the research methodology and the methods used to collect data?</td>
<td>Yes, the method used to collect data was consistent with research methodology.</td>
</tr>
<tr>
<td>4. Is there congruity between the research methodology and the representation and analysis of data?</td>
<td>Yes, there was congruity between the research methodology and the representation and analysis of data.</td>
</tr>
<tr>
<td>5. Is there congruity between the research methodology and the interpretation of results?</td>
<td>Yes, and interpretations were made adequately.</td>
</tr>
<tr>
<td>6. Is there a statement locating the researcher culturally or theoretically?</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>7. Is the influence of the researcher on the research, and vice- versa, addressed?</td>
<td>Yes, it was discussed.</td>
</tr>
<tr>
<td>8. Are participants, and their voices, adequately represented?</td>
<td>Yes, Consolidated Criteria for Reporting Qualitative Research (COREQ) was applied.</td>
</tr>
<tr>
<td>9. Is the research ethical according to current criteria or, for recent studies,</td>
<td>Yes, permissions to carry out the study was taken from ethics committees of six universities.</td>
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and is there evidence of ethical approval by an appropriate body?

10. Does the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?  

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<th>Question</th>
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<tr>
<td>and is there evidence of ethical approval by an appropriate body?</td>
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<tr>
<td>10. Does the conclusions drawn in the research report flow from the</td>
<td>Yes, a conclusion was drawn in the research report.</td>
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<td>analysis, or interpretation, of the data?</td>
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**Overall Quality:**

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<th>Quality</th>
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<tr>
<td>Author and Year</td>
<td>Campbell et al, 2009</td>
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<tr>
<td><strong>Comments:</strong></td>
<td>(Yes, No, Unclear, Not applicable)</td>
</tr>
<tr>
<td>1. Is the source of the opinion clearly identified?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Does the source of opinion have standing in the field of expertise?</td>
<td>Yes</td>
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<tr>
<td>3. Are the interests of the relevant population the central focus of the opinion?</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Is the stated position the result of an analytical process, and is there logic in the opinion expressed?</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Is there reference to the extant literature?</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Is any incongruence with the literature/sources logically defended?</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Overall Quality:</strong></td>
<td>Include/Exclude/Seek further information</td>
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<tr>
<td><strong>Overall Quality:</strong></td>
<td>Include</td>
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Chapter 3: Pakistan Context

Pakistan came into being on 14th August 1047. The country was created following the largest migration of Muslims from the Indian sub-continent to become citizens of Pakistan. There was migration in both directions with hindus and sikhs moving in the opposite direction to India. There has remained deep rooted conflict between the two States (India and Pakistan) which have resulted in two full scale wars. This historical conflict remains and has consequently resulted in geo-political instability in the region. Pakistan was created as an Islamic State and 95% of the population practice Islam, despite the shared religion there is diversity of cultures and languages in the five provinces. This diversity has caused rivalries between the provinces and has manifested in regional tensions. Throughout its history, Pakistan has oscillated between military and democratic rule. The current situation is that the Pakistani people have lost faith in the democratic system. It is felt to be corrupt and chaotic resulting in economic and social turmoil. The recent natural disasters have propagated the situation. On the one hand, the Pakistani people face these dilemmas. However, on the other hand the resilience and perseverance of the nation continues to offer the world traditions that are colourful and rich culturally, intellectually, and religiously.

According to Moazam and Jafarey, 2005, the culture of Pakistan is complex with a mix of many ethnicities and subcultures. The religious values and family centredness means that the ‘family extends beyond the nuclear’ (Moazam and Jafarey, 2005) where it not uncommon to have three generations living under the same roof. Free of charge healthcare does exist through the government. However, demand hugely surpasses supply. On the other hand, the flourishing private healthcare remains beyond the reach of the majority of the population due to poverty. Most of the medical community, although a biproduct of a culture of Islamic beliefs and values, having trained on the western biomedical model are beginning to interconnect with modern bioethics. International collaborations and the focus of funding agencies and peer reviewed journals has begun to strengthen the development of research.
and health ethics in Pakistan. Globalisation and technological advances in medicine has instigated interest in biomedical ethics. There are numerous capacity building programs which are not just focussing on the western bioethical aspects and the four bioethical principles but also investigating traditional muslim opinion sources and views of muslim scholars on topics such as organ transplantation, brain death criteria and death and dying (Moazam and Jafarey, 2005). More recently, there have been developments by the medical community to propagate a discourse on how modern ethics could link with the Pakistani cultural and (Islamic) beliefs, moral values and socioeconomic ‘real world’ situation. Moazam and Jafarey state that “the biotechnology in Pakistan may be identical to that in the West, but it is being applied in a country with a very different epistemology of what constitutes right and wrong and how this is to be determined”.

According to Collins Dictionary, cultural context refers to the environment, customs and norms that effect on the attitudes, behaviour and values of the people who live in that particular society. To contextualise my research, it was important to examine the current health and research ethics discourse in Pakistan as well as proceed to look at literature on Islamic approach to research ethics.

3.1 Health and Research Ethics in Pakistan

In order to comprehend the current understanding of bioethics and the challenges to utilisation of the western bioethical principles in a different cultural, religious and social context a narrative review of the health ethics literature in Pakistan was carried out. I would like to acknowledge the input of my researcher colleague, Ms Muqaddas Asif (MA), who helped with the literature search and quality assessment of the studies.

The aim of this narrative review was to gauge the extent to which bioethics is part of professional or academic culture in Pakistan. Bioethics relates ethics to health policy and health systems research, public health research and clinical research (Hyder et al., 2014). The following review describes the current state
of health ethics in health care institutions in Pakistan as far as it has been assessed and published in peer reviewed journals. Constructive dialogue with greater understanding of ethical issues within regional and national contexts may lead to better solutions to ethical issues for both healthcare providers and patients in LMIC, such as Pakistan (Hyder et al., 2001). Ethical standards including appropriate training, expertise and care are strongly advocated for health care professionals. All physicians are obliged to adhere to these ethical standards (Atighetchi, 2007). Codes of ethics are vital in differentiating a profession from everyday morality (Hedgecoe, 2004), although ethical violations in the health sector can be protected by lack of transparency in health care system and inefficiency of regulatory bodies. Trust of the patients is thought to be breached routinely but rarely reported among the LMICs (Riaz, Khan and Jafar, 2017). In government hospitals, healthcare is provided free of cost, but these hospitals often do not have sufficient staff, they are generally overcrowded, inefficient, and many of these have been known to provide sub-standard health care (Moazam and Jafarey, 2005). Over the past few decades, private healthcare institutions have proliferated across Pakistan, especially in urban areas. On the other hand, due to widespread poverty and lack of health insurance schemes, these services remain beyond the reach of the majority of the country’s population.

National Bioethics Committee (NBC) of Pakistan is the major official body established in 2004 to set and sustain the principles of bioethics in all divisions of healthcare. NBC enforces applicable laws and code of practice, values, and principles. The primary function of the NBC is to promote and facilitate ethical health service delivery and health research. This multidisciplinary and multi-sectoral committee is composed of many disciplines of medicine with relevant expertise, and well-respected non-medical people representing the interests and concerns of the community. The NBC has two sub committees: 1) Research Ethics Committee (REC) and 2) Healthcare Ethics Committee (HCEC). The primary responsibility of REC is to review multinational funded research proposals and HCEC is responsible
for bioethics education in research and clinical medicine in all provinces of Pakistan (NBC, 2021) It is currently working on developing ethical guidelines to help with ethical dilemmas facing institutions in the current context of Covid-19 (NBC, 2020). It is an umbrella body that is linked with professional bodies such as Pakistan Medical and Dental Council (PMDC), the Medical Training and Teaching Institutions and Universities and the recently constituted Good Clinical Practice (GCP) committee of the Ministry of Health’s Drug Division. Most of the educational universities now have an independent Institutional Review Board (IRB). All research being conducted by students must first be approved by the review board of their relevant departments. Clinical ethics committees at hospital level are however still rare in Pakistan.

The concept of mandatory ethics approval by Ethics Review Committee (ERC) or IRBs for research projects involving human subjects is gradually emerging in Pakistan, and recently the medical community has begun to recognise its importance (Jafarey, Iqbal and Hassan, 2021). Ethics in health research has gained increased recognition and importance internationally. Hence, collaborative partnerships in research projects with international institutions and organisations such as WHO, and for publications in international indexed journals has necessitated this. Although health ethics is being given more prominence in Pakistan, the curriculum of ethics or bioethics is not (yet) taught at college level or in universities as a separate subject (Khan et al., 2012). The health care system is at a crossroad and is facing many challenges in practice. This review aims to document the current nature of health ethics in the Pakistan healthcare system.

Review Question

What is the current state and practical implications of health ethics in the healthcare system in Pakistan?
Methods

Search methods for identification of studies

Literature search was conducted by searching electronic databases: Google scholar, Science direct and PubMed. To add breadth, manual searches from reference lists of identified studies were done to find more studies eligible for literature review. Literature search was restricted from January 2001 to December 2019 as one such literature review (1988-1999) was found. Hence, my study focused the literature search from 2001 to date. Searched articles were reviewed and evaluated for selection.

Search Strategy

Literature search was conducted by searching electronic databases, Google scholar, Science direct and PubMed. Electronic databases were searched using search strategy based on a combination of the following terms:

‘Health ethics’ OR ‘medical ethics’ OR ‘biomedical ethics’ OR ‘bioethics’ AND ‘Pakistan’. The search was run in January 2020. Following the search, the searched articles were reviewed and evaluated for selection.

a) Inclusion criteria

Only those articles reporting empirical data to inform an assessment of biomedical ethics in Pakistan were included. Both quantitative and qualitative studies were included.

b) Exclusion criteria

All those studies based on opinion, commentaries and discussions were excluded. Studies were assessed for relevance of research question and study design.

Results

Two independent reviewers’ MA and I (RM) did screenings and data extraction of included studies according to the PRISMA diagram. Disagreements were resolved through discussions between the two
reviewers. The basic information extracted from each included study contained the first author, year of publication, title, objective, study design, population, sample size, response rate and findings. A summary of main findings of studies have been presented in table 2.
The review of literature revealed a total of 20 studies related to health ethics in Pakistan from all electronic and manual searches. A total of ten studies in public and private hospital settings met the inclusion criteria of which seven studies were cross-sectional, one survey and two qualitative studies. Of the ten studies, seven were service specific and three related to clinical practice. Of those excluded, two studies were reports, six editorial papers and two previous literature reviews. We did not include the literature reviews as they did not include empirical data. The results covered in the review relate specifically to equipoise in the following ways:

1. Duty of Care and Freedman’s original idea of collective equipoise
2. Training and knowledge of codes so clinicians’ views on equipoise can be interpreted.
3. Oversight of research to show extent of cultural check on research ethics.

3.1.1 Quality assessment of included studies.

Two researchers (MA and RM) performed quality assessment of included studies independently. For quality assessment of studies, British Sociology Association (BSA) Medical Sociology Group checklist (Blaxter, 1996) for cross-sectional and survey studies (see table 3) was used. The Joanna Briggs Institute (JBI) critical appraisal tools for qualitative studies (Lockwood et al., 2015) (see table 3a,3b) were adapted and used for this review.

Key evaluation of the quality of evidence is also provided as shown in Table x. The review findings are presented as a narrative synthesis below:

3.1.1a Duty of Care

The duty of care legislation makes it obligatory for a healthcare professional to adhere to a standard procedure of care to ensure the safety and wellbeing of patients. According to Shiwani and Gadit opinion paper (2011), Pakistan has witnessed several cases of medical negligence i.e., failure to meet standards of care (Grober and Bohnen, 2012). A qualitative study (Jafree et al., 2015) conducted with female nurses in Pakistan revealed that patients are
unwillingly receiving treatment from nursing staff or medical students with no evidence of obtaining informed consent for non-surgical procedures and to accept treatment from (under trained staff) nursing students. Sheikh and Humayun (2012) reported that nearly 70% of surgeons are not fully aware of what malpractice means. Malpractice is a failure to act correctly and legally when doing one’s job, often causing injury or loss, while negligence is practice which does not meet certain expected reasonable standards. However, the majority of surgeons (90.9%) do not report surgical errors due to fear of blame or legal action, while some (26.0%) do not accept complicated cases which may be risky. Discriminating patients, blame shifting, and non-reporting of errors has been observed in another study (Jafree et al., 2015). However, it is not reported how often these practices have been observed and when asked, patients said that they are never asked about quality of care provided (Imam et al., 2007).

A number of studies have been conducted to look at the ethical integrity of healthcare professionals, perception and experiences of patients and deficiencies in health care provision. Financial gain held more value over duty of care only for a minority (8.5%) of self-reporting professionals (Sheikh and Humayun, 2012). Limited knowledge, lack of professional competence, professional trustworthiness, and poor accountability put together are responsible for hampering ethical practices (Afandi, Ismail and Purwadianto, 2011). According to Sheikh and Humayun (2012), variable medical practice and financial gain above patient welfare remains a threat to ethical practice. There are clear guidelines on interaction with the pharmaceutical industry by PMDC, but unfortunately most graduates of healthcare are unaware that such guidelines exist (Tahir, Yasmin and Khan, 2018). Corruption in health care sector affects all LMICs. Youzafzai (2015) in his editorial paper mentioned that in Pakistan, corruption in medical practice including ordering unnecessary investigations and procedures, commissions; significant absenteeism, and conflict of interest within the physician-pharmaceutical nexus is preventing people from having access to good quality health care.
3.1.1b Knowledge of code of ethics

It is the duty of health professionals to be aware of the code of ethics in carrying out their responsibilities with accuracy, competency, honesty, and transparency. The PMDC is the registering body for doctors and dentists in Pakistan. One study identified in this review, revealed that most of the health professionals do not know the codes of ethics of the PMDC (Shairaz et al., 2005). Strikingly, doctors graduating within the last ten years have less knowledge of ethics than those graduating earlier (Shairaz et al., 2005). The lack of knowledge of ethical guidelines also give rise to unethical practices in interactions with pharmaceutical companies (Tahir et al. 2013). Health professionals often face ethical complications and dilemmas due to lack of rigorous training; this ultimately results in different opinions about ethical issues (Leap et al., 2009). In recent years the knowledge and practice of ethics codes among doctors has been inadequate (Riaz, Khan and Jafar, 2017).

3.1.1c Ethics Education for Healthcare Professionals

The concept of mandatory ethical review of research involving human participants is gradually taking root in Pakistan, but inconsistency in ethical guidelines and variable opinions of IRB members across the country make the review process challenging (Khan et al., 2012). Lack of registration or accreditation for IRBs has also resulted in variable standards of these boards. Researchers and medical staff are not properly trained which is the main challenge (Khan et al., 2012). The reliability of the review process is greatly destabilised by external pressure and influence, conflicts of interest and discrepant requirements of review for ethics approval of research remains a challenge. Institutional leadership itself is thought to be a significant threat to independent functioning of such review boards. The review process must be uniform, consistent and trustworthy to gain the respect of researchers. Otherwise, IRBs could become no more than rubber stamping committees (Jafarey, Iqbal and Hassan, 2012).
PMDC in 2001 agreed on the need of biomedical ethics in daily practice and ruled that biomedical ethics must be part of all medical curriculum. However, the majority of the country’s medical colleges do not consider it to be essential (Haider et al, 2014). Teaching of medical ethics has a strong influence on clinical practice and attitudes in the health care sector. Health professionals have not been taught ethics as a subject (Shaikh and Humayun, 2012; Shairaz et al., 2005), consequently they have difficulties when facing many ethical dilemmas in their daily practice (Imran et al. 2014). Farooq et al (2018) observed that a significant gap exists in the application of the knowledge of medical ethics in the clinical setting. The current training level of professionals is not enough for ethical decision making.

As in the western world, the focus on ethics is increasing (Khan et al. 2012). In developed and developing countries, maintenance of highest ethical standards in research and practice is a challenging task (Varmus and Satcher, 1997). A survey design study with residents, registrars, specialists and interns in Pakistan reported that out of 101, only 51 clinicians have heard about the code on bioethics (Shairaz et al., 2005) and implementation of ethical guidelines in clinical practice is almost non-existent (Shaikh and Humayun, 2012). Although, the number of healthcare professionals with formal bioethics degrees in the country is increasing but a majority of them still remain lacking in bioethics training (Jafarey, Iqbal and Hassan, 2012).

There is an urgent need to establish an ethical framework for LMICs like Pakistan. Rigorous systems and processes are needed to be put in place to eliminate the physician/pharmaceutical ties and to reduce unwarranted variation in the quality of medical care provision. In order to achieve this, collaborative efforts by the government, healthcare sector, and ethics regulatory bodies is paramount. Recent international reports have concentrated on the appropriate and ethical research conduct but this has not been a focus in the papers published in Pakistan. A richer discussion in both real settings and scientific literature to stimulate consideration of ethics in the field of health policy development and biomedical research is required,
especially in developing countries like Pakistan. This gap appears challenging, but it also provides an opportunity, particularly when there is emerging leadership within the country, to develop a robust medical ethics framework which is fit for purpose for the cultural and religious context of Pakistan. An important step towards achieving this has been the former government’s leadership in initiating health care access to all such as the Prime Minister’s ‘Sehat Sahulat’ social welfare program (www.pmhealthprogram.gov.pk). For quality assurance, mandating medical and research ethics to be a key component of the curriculum is essential, so that the four bioethical principles of beneficence, non-maleficence, autonomy, and justice are embedded in the daily medical practice of doctors and researchers in order to safeguard the interest and welfare of their patients and study subjects.

Quality assessment rating was high for five studies and moderate for five studies.
Table 2: Empirical Studies showing results of biomedical ethics in Pakistan

<table>
<thead>
<tr>
<th>Author(s) (Year)</th>
<th>Title</th>
<th>Objective</th>
<th>Study design</th>
<th>Population</th>
<th>Sample Size</th>
<th>Response rate</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiraz et al. (2005)</td>
<td>Medical ethics in surgical wards: knowledge, attitude and practice of medical ethics among surgical team members in Karachi.</td>
<td>To assess the knowledge, attitude and practice of medical ethics among surgical team members of university hospitals</td>
<td>Survey design</td>
<td>Residents, Registrars, specialists and interns.</td>
<td>N=101 (n=68 male, n=33 female)</td>
<td>101/120</td>
<td>About half (51 out of 101) of the respondents had heard about the Code of Ethics. 44 of the respondents read these codes while seven of them had no information about code of ethics. 47 reported that they are used to take consent for procedures. Only 11 respondents reported that they have been taught ethics as students. Four did not feel the need to teach</td>
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</tbody>
</table>
Humayun et al. (2008) Patients' perception and actual practice of informed consent, privacy and confidentiality in general medical outpatient departments of two tertiary hospitals. To explore the degree of ethical practices of informed consent, privacy and confidentiality in medical outpatient departments of public and private sectors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>N=186</th>
<th>Not given</th>
<th>Informed consent was obtained from 9.7% of patients in public hospitals as compared to 47.8% in private. Confidentiality was maintained in 10.8% and 35.5% in public and private sectors respectively.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humayun et al. (2008)</td>
<td>Cross-sectional study</td>
<td>Patients selected from general medical out-patient departments</td>
<td>n=138</td>
<td>n=48</td>
<td>male</td>
</tr>
<tr>
<td>study</td>
<td>researchers</td>
<td>objective</td>
<td>population</td>
<td>sample size</td>
<td>findings</td>
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<tr>
<td>Imran et al. (2014)</td>
<td>Health ethics education: knowledge, attitudes and practice of healthcare ethics among interns and residents in Pakistan</td>
<td>To study the knowledge, attitudes and practices of junior physicians about healthcare ethics</td>
<td>Interns (183), junior (130) and senior postgraduate trainees (85)</td>
<td>N = 398 (n = 58% male, n = 42% female)</td>
<td>A high proportion of respondents (57%) had no knowledge of code of ethics of Pakistan Medical and Dental council. A few of them i.e. 7% interns and junior residents; 14% senior residents knew about Helsinki declaration. Junior doctors face ethical dilemmas on regular basis but their training level is insufficient to help them.</td>
</tr>
<tr>
<td>Jafree et al. (2015)</td>
<td>Ethical violations in the clinical setting: the hidden curriculum learning experience of Pakistani nurses</td>
<td>To identify those aspects of the hidden curriculum which encourage ethical violations in the clinical setting</td>
<td>Deductive qualitative research design (twenty interview Four focus groups)</td>
<td>Female registered nurse and nurse students</td>
<td>N= 42 female nurses</td>
</tr>
<tr>
<td>Riaz et al. (2012)</td>
<td>Ethics in Health Care settings: Practices of Healthcare Professionals and Perceptions of Patients regarding Informed Consent, Confidentiality and Privacy at Two Tertiary Care Hospitals</td>
<td>To explore the practices of doctors and perceptions of patients regarding informed consent, confidentiality and clinical practice in clinical setup</td>
<td>Qualitative study design</td>
<td>Doctors and patients</td>
<td>N= 8 focus groups each with 6-8 participants (4 at public hospitals and 4 at private hospitals)</td>
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</tbody>
</table>
As the study was qualitative with content analysis, quantitative descriptions were not given.

<table>
<thead>
<tr>
<th>Tahir et al. (2013)</th>
<th>Attitude and practice of dental surgeons towards pharmaceutical companies’ marketing gifts.</th>
<th>To explore the attitudes and practices of fresh dental graduates, faculty members and private practitioner’s in dentistry towards pharmaceutical gifts</th>
<th>Cross-sectional design</th>
<th>Fresh graduates, residents/ faculty members and private practitioners</th>
<th>N= 209 dentists</th>
<th>209/220</th>
</tr>
</thead>
</table>

During last three months, 89.6% of private practitioners (PPs) had been visited by pharmaceutical representatives as compared to 62.8% of fresh graduates and faculty members. A high percentage of (69%) PPs accept gifts from pharmaceuticals against 43.1% of faculty members. However mostly (65%) PPs
recognised them as unethical. Both groups (over 70%) considered sponsoring of on campus lectures as acceptable

Sheikh et al. (2012) Malpractice awareness among surgeons at a teaching hospital in Pakistan

To evaluate the knowledge, attitudes and practices of surgeons regarding malpractice at a tertiary care centre

Cross-sectional study

Surgeons N= 319 (n = 148 from inpatient departments n = 171 from outpatient department) 319/400

More than half (68.7%) of surgeons were unaware of malpractice definition. The study revealed different forms of malpractices among surgeons. Moreover, it was observed that medical error is not reported usually due to threat of assault or claim. Majority 75.5% took informed consent for operating surgery
and a few, 26.0% expressed that they are reluctant to accept complicated cases. Study revealed that liabilities and financial gains as a source of biasness in care.

<p>| Jawaid et al. (2012) | Preoperative Informed Consent: Is It truly informed? | To assess the practice of preoperative informed consent | Observational study design | Patients from General Surgery, Orthopedics, Ear Nose &amp; Throat and Ophthalmology | N = 350 (n = 217 male, n = 133 female) | Result of study highlighted that a few (3.6%) patients were informed about complications of surgical procedure and risks of anesthesia (4.9%). Half of the participants were satisfied from the information provided for informed consent. However, quality of | 350/350 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Participants</th>
<th>N (%)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farooq et al. (2018)</td>
<td>Awareness of medical ethics principles and their applications among healthcare professionals in Pakistan</td>
<td>Cross-sectional study</td>
<td>N= 243</td>
<td>There were significant differences (p&lt; .05) in awareness about clinical concepts in physicians from public vs private medical colleges. 60% from private and 40% from public hospital were aware of confidentiality; 63.2% from private and 36.8% from public were aware of non-maleficence; 58% from private and 42% from public were aware of Informed</td>
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</tbody>
</table>
Consent, 58.3% from private and 41.7% from public were aware of respect for privacy, 58.8% from private and 41.2% from public were aware of desirable attitudes. 48.4% of respondents said that they had read PMDC code of ethics at some point in their career but 51.2% of them said that they haven’t read.

Imam et al. (2007) Patients’ satisfaction and opinions of their experiences To identify and address unsatisfactory factors in the cross-sectional study Inpatients with at least one day of admission N= 173 inpatients Majority of patients (68.6%) expressed that they have been never asked about views on quality of care provided,
during admission in a tertiary care hospital in Pakistan – a cross sectional study they provide. 

| m = 5.27 days of hospital stay | 20% of the patients did not find opportunity to talk to about their worries and 27.6% were given emotional support to only at some extent. |
Table 3: Checklist for quality assessment of cross-sectional studies

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<tbody>
<tr>
<td>Imam et al. (2007)</td>
<td>Yes, cross-sectional study was designed.</td>
<td>Yes, inclusion exclusion criteria were defined and followed to recruit participants in the study.</td>
<td>Yes, response rate was given.</td>
<td>Yes, sample was representative.</td>
<td>Yes, a peer reviewed translation of valid measure was done and that was used for data collection.</td>
<td>No, justification of sample size was not given.</td>
<td>No, they just compute frequencies and percentages and then subjectively compared data.</td>
<td>5(Moderate)</td>
</tr>
<tr>
<td>Imran et al. (2014)</td>
<td>Yes, research design was appropriate.</td>
<td>Yes, recruitment strategy was appropriate.</td>
<td>Yes, response rate was mentioned.</td>
<td>Yes, sample was representative.</td>
<td>Yes, they used a valid objective measure.</td>
<td>No, power calculation was not given.</td>
<td>No, only frequencies of the</td>
<td>5(Moderate)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Recruitment Strategy</td>
<td>Response Rate</td>
<td>Sample Representativeness</td>
<td>Assessment</td>
<td>Justification of Numbers</td>
<td>Statistical Analysis</td>
<td>Summary</td>
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<tr>
<td>Jawaid et al. (2012)</td>
<td>Yes, it was observational investigation.</td>
<td>Yes, it was appropriate.</td>
<td>No, it was not given.</td>
<td>Yes, it was representative.</td>
<td>No, they used a few structured questions which participants responded in yes or no.</td>
<td>No, it was not given.</td>
<td>No, they just calculated frequencies and percentages.</td>
<td>3 (Moderate)</td>
</tr>
<tr>
<td>Humayun et al. (2008)</td>
<td>Yes, research design (cross-sectional) was appropriate as the study</td>
<td>Yes, recruitment strategy was appropriate as using systematic random sampling,</td>
<td>No, response rate was not given.</td>
<td>Yes, sample was representative and participants were approached through OPD records.</td>
<td>Yes, assessment was undertaken in a subjective manner but each doctor-</td>
<td>Yes, justification of numbers was given. To, assume the patient perception of good ethical</td>
<td>Yes, statistical analysis was appropriate.</td>
<td>6 (High)</td>
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68
aimed to explore the degree of ethical practices in medical outpatient departments in public and Private hospitals. Patient interaction was observed and evaluated, to fill a peer-reviewed client flow analysis form created in the light of existing literature on the subject with yes or no questions. Patient attendance at the General medical OPD was selected and in case patient refused consent, next patient was approached using the same strategy. Practices to be 55% at 0.05 significance level, a sample of 93 patients was required from each hospital. Any significant differences public and private hospitals.
<table>
<thead>
<tr>
<th>Study</th>
<th>Research Design</th>
<th>Recruitment Strategy</th>
<th>Response Rate</th>
<th>Sample Representativeness</th>
<th>Assessment Tool</th>
<th>Power Calculation</th>
<th>Analysis</th>
<th>Data Nature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tahir et al. (2013)</td>
<td>Yes, cross-sectional research design was appropriate</td>
<td>No, recruitment strategy of sample was not given.</td>
<td>Yes, response rate was given. Out of 220 participants, 209 (95%) completed study instrument.</td>
<td>Yes, sample was representative of population.</td>
<td>Yes, The assessment tool was a questionnaire that was designed based on previously published studies in India and Norway.</td>
<td>No, power calculation was not given but the sample was based on the expected representative size.</td>
<td>Yes, as data was mostly qualitative, so percentages were given.</td>
<td>5(Moderate)</td>
</tr>
<tr>
<td>Shairaz et al. (2005)</td>
<td>Yes, research design was appropriate.</td>
<td>Yes, recruitment strategy was appropriate as</td>
<td>Yes, response rate was given. 101 out of 120</td>
<td>No. sample was not representative and convenient</td>
<td>Yes, a standardized questionnaire was developed</td>
<td>No, power calculation was not given.</td>
<td>Yes, analysis was appropriate as Chi square test</td>
<td>5(Moderate)</td>
</tr>
<tr>
<td>Study</td>
<td>Design Appropriateness</td>
<td>Participants</td>
<td>Responses</td>
<td>Sampling</td>
<td>Data Collection</td>
<td>Analysis</td>
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<tr>
<td>Farooq et al. (2018)</td>
<td>Yes</td>
<td>Yes, randomly selected from public and private sector hospitals.</td>
<td>Yes, a total of 230 from 243 answered complete questions.</td>
<td>Yes, Sample was representative.</td>
<td>Objective was clear but they used self-constructed objectives as questions.</td>
<td>Yes, sample size justification was given.</td>
<td></td>
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<tr>
<td>Shiekh et al. (2012)</td>
<td>Yes</td>
<td>Yes, all surgeons of the hospital were included.</td>
<td>Yes, it was given.</td>
<td>No, only one hospital was approached for sample.</td>
<td>Yes, they have clear objectives and used self.</td>
<td>Yes, they tried to include surgeons.</td>
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</tbody>
</table>

Yes, study design was appropriate according to study objective. Yes, study design was appropriate according to study objective. Yes, sample size justification was given. Yes, analysis was adequate. 6 (High)
constructed from all departments. of association between variables.

Note: ** Y=Yes N=No [Quality Indicators Met out of 7: 1-2 (Low) ---- 3-5 (Moderate) ----6-7 (High)]
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Riaz et al. (2017)</th>
<th>Comments: (Yes, No, Unclear, Not applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Is there congruity between the stated/theoretical perspective/rationale and the research methodology?</td>
<td><strong>Yes,</strong> the study highlighted the need to study ethical practices of doctors and health professionals to identify issues and enabling factors that could lead to proper implication and practice of health ethics. Qualitative study methodology was appropriate to address this issue.</td>
<td></td>
</tr>
<tr>
<td><strong>2.</strong> Is there congruity between the research methodology and the research question or objectives?</td>
<td><strong>Yes,</strong> the research methodology was in accord with the study objective as the study addresses the objective of exploring ethical practices of doctors and perceptions of patients regarding these practices through focus group discussions.</td>
<td></td>
</tr>
<tr>
<td><strong>3.</strong> Is there congruity between the research methodology and the methods used to collect data?</td>
<td><strong>Yes,</strong> the method used to collect data was consistent with research methodology as data was collected through focus group discussions with doctors and patients attending the hospital. Patients from both genders were interviewed.</td>
<td></td>
</tr>
<tr>
<td><strong>4.</strong> Is there congruity between the research methodology and the representation and analysis of data?</td>
<td><strong>Yes,</strong> data was collected from both the doctors and patients and eight homogenous focus groups were conducted and analysed using content analysis.</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>5. Is there congruity between the research methodology and the interpretation of results?</td>
<td>Yes, data was interpreted over the identified themes of ethical practices in health care settings. Results were presented adequately.</td>
<td></td>
</tr>
<tr>
<td>6. Is there a statement locating the researcher culturally or theoretically?</td>
<td>Not applicable.</td>
<td></td>
</tr>
<tr>
<td>7. Is the influence of the researcher on the research, and vice-versa, addressed?</td>
<td>No. it was not discussed.</td>
<td></td>
</tr>
<tr>
<td>8. Are participants, and their voices, adequately represented?</td>
<td>Yes, to ensure participants representation, illustrations from data were given and conclusions were drawn on the basis of those statements.</td>
<td></td>
</tr>
<tr>
<td>9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?</td>
<td>Yes, permissions to carry out the study was taken from Internal Review Board (IRB) of Health Services Academy (HSA), Islamabad, from participants and hospital authorities.</td>
<td></td>
</tr>
<tr>
<td>10. Does the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?</td>
<td>Yes, considering the findings of the study, a conclusion was drawn in the research report.</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Quality:**
High

Low/Moderate/High
**Table 3b: Checklist for quality assessment of qualitative studies**

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Jafree, et al. (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments: (Yes, No, Unclear, Not applicable)</td>
<td></td>
</tr>
<tr>
<td>1. Is there congruity between the stated theoretical perspective/ rationale and the research methodology?</td>
<td>Yes, research methodology and rationale of the study was in congruity as the study focused on hidden curriculum learning experiences of nurses to explore ethical violations in clinical setting through qualitative research methodology.</td>
</tr>
<tr>
<td>2. Is there congruity between the research methodology and the research question or objectives?</td>
<td>Yes, the study research methodology was appropriate according to research objective as the study aimed to identify aspects of hidden curriculum which encourage ethical violations in the clinical setting. Qualitative interviews and focus group discussions of nurse’s experiences during clinical practice were conducted.</td>
</tr>
<tr>
<td>3. Is there congruity between the research methodology and the methods used to collect data?</td>
<td>Yes, as data was collected through qualitative interviews and focus group discussions from willing female registered nurses and registered nurse students. Hospitals were randomly selected for data collection.</td>
</tr>
<tr>
<td>4. Is there congruity between the research methodology and the representation and analysis of data?</td>
<td>Yes, data was analysed using deductive qualitative approach through content analysis of data. Sub-categories were identified from pre-defined categories of nursing code of ethics.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5. Is there congruity between the research methodology and the interpretation of results?</td>
<td>Yes, data was interpreted appropriately. Final categories and reliability of findings was assured by multiple coding of researchers and respondent validation.</td>
</tr>
<tr>
<td>6. Is there a statement locating the researcher culturally or theoretically?</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>7. Is the influence of the researcher on the research, and vice-versa, addressed?</td>
<td>No. it was not discussed.</td>
</tr>
<tr>
<td>8. Are participants, and their voices, adequately represented?</td>
<td>Yes, illustrations of participants from the data were presented.</td>
</tr>
<tr>
<td>9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?</td>
<td>Yes, the overall study was ethical and ethical approval for study was collected from hospitals and nursing institutes.</td>
</tr>
<tr>
<td>10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?</td>
<td>Yes, a proper conclusion following findings and interpretations was drawn by researcher.</td>
</tr>
</tbody>
</table>

**Overall Quality:**  
High
3.2 Islamic Approaches to Research Ethics

As my research is set in Pakistan which is predominantly an Islamic country. I felt it would be of merit to research Islamic perspectives of research ethics, with a view to begin a conversation towards conceptualising a culturally and socially relevant approach towards medical research ethics in Pakistan. The Islamic Republic of Pakistan was founded in 1947, and is the only country created on the basis of Islam (Newcomb, 1986). The population is over 95% Muslim, and the Islamic doctrine is engrained in the culture and traditions of the country. For that reason, it is fundamental to explore the religious doctrine and its influences on the beliefs, cultural nuances, norms and values underpinning people’s behaviour and practice. This section attempts firstly, to describe the Islamic ethical framework and the salient features of the purist basis of Islamic ethics i.e., Shariah Law. Secondly, it examines Ijtihad and Usul-Al-Fiqh, the Islamic process and methodology for arriving at the ‘correct decision’ and finally proposes Adab (Sufi attitude and behaviour) as a complementary virtue based approach to the obligation based approach (shariah) in an endeavour to modernise and rediscover Islamic principles, which embrace the cultural and social nuances of South Asia and the Indian sub-continent.

The worldwide Muslim population is growing, and is expected to grow to 2.2 billion by 2030 (Grim and Karim, 2011). According to Padela (2019), since nearly a quarter of the world’s population follows the Islamic ethical doctrine, it is important to have a discourse on the different Islamic disciplines such as Adab (virtue-based ethics), law and philosophy and how this scholarly debate can help inform the development of Islamic bioethical guidelines. Moreover, increase in the Muslim population makes it likely that more and more clinicians will provide care to Muslim patients at some time during their career.

Niyozov and Memon in their review (2011) report that recognition of Muslim students’ diverse backgrounds and the need for cultural
sensitivity in curriculum design will help engage Islam and its religious and cultural practices. Cultural aspects and cultural adaptations have been a more traditional line of thought in research. However, in the Muslim population religiosity requires particular attention in medical research (Altalib et al., 2019). The Islamic belief is that religion should be encapsulated in all physical and emotional behaviour. Hence, the conduct of the Muslim individual is an important factor to be explored within the discourse of research ethics.

3.2.1 Building Blocks of the Ethical Principles of Islam

The overall objective of Islam is for people to be good human beings and with their good deeds, to make this world a better place for everyone. The Islamic approach is governed by two sources; the Quran – the Holy Book from God which was revealed to the Holy Prophet (Peace Be upon Him (PBH)) as an Islamic text for his Ummat (Muslims), on the principles and practice of daily living. Muslims believe that the miracle of Quran is its eternal relevance. The second source is the Hadith – the teachings and the practice of the Holy Prophet (PBH) as a code of conduct on the practice of Islam. The founding principle of Islam is that ‘it is a way of life’ (Saeed, 2001). In other words, as a Muslim, faith and religion are not divorced from the daily activities but are part and parcel of an individual’s everyday practice in all walks of their life.

“His (Allah) commands permeate through all aspects of a Muslim individual’s daily activities” (Nadwi, 1978). Therefore, all actions are considered as worship (ibadah) of Allah (Saeed et al., 2001). According to the Muslim belief, goals and principles are legally enshrined in ‘Shariah’.

3.2.2 Shariah law

The term Shariah means ‘the path to salvation’ (Sartell and Padela, 2015) referring to the welfare of the individual in all walks of life. The ethico-legal construct of the Shariah is underpinned by the fundamental
belief that all acts are carried out by the will of Allah for the service of God and for the welfare of humanity.

The five goals of Shariah Law are:

(i) **Protection of life (beneficence and non-maleficence)**

Life is a gift from Allah and the sanctity of preserving life, both one's own life as well as that of others is obligatory in Islam. Aggression, humiliation and harm is absolutely forbidden. Allah says:

“In the law of equality there is (saving of) life to you, O ye men of understanding, that you may restrain yourselves” (Holy Quran 2:179).

The gift of life is bestowed upon human beings by Allah to carry out the duties of protecting self and others on this earth. With this also comes the duty to protect the poor, disabled and the vulnerable and that their needs and rights are catered for. Allah forbids harm to others and He says:

“and those who annoy believing men and women' undeservedly bear (on themselves) a calumny and a glaring sin” (Holy Quran 33.58).

Regarding the value of Beneficence and Non-maleficence or doing no harm. Prophet Mohammed (PBH) said “There should be neither harming nor reciprocating harm.” ("Sunan Ibn Majah 2341, Book 13, Hadith 34,"). He also said “Allah likes when any one does any work, to do it with perfection” (Imam Al Baihaqi).

Preservation of life, one's own as well as of others is a command from Allah. Suicide is forbidden in Islam. Allah says:

“Do not kill yourself. No doubt Allah is merciful and anyone who does so, will be pushed in fire. And it is easy for Allah” (Holy Quran 4:29, 4:30).
(ii) **Protection of mind and dignity**

Human beings have been given the mind, so that they reason to conduct both religious and secular duties. Through sound reasoning and guidance, the individual discovers great facts rather than has blind faith (Baksh, 2013). Allah says:

“Or have they taken for worship (other) gods besides Him.” Say “Bring your convincing proof” (Holy Quran 21:24).

Education and the pursuit of knowledge is the command of Allah.

In the first verse of Quran Allah says:

“Read, read in the name of thy Lord who created; (He) created the human being from blood clot. Read in the name of thy Lord who taught by the pen; (He) taught the human being what he did not know” (Holy Quran 96: 1-5).

Allah also says in the Quran:

“Are those who have knowledge equal to those who do not have knowledge?!" (39:9)

(iii) **Protection of religious practice (autonomy)**

Autonomy and the free will to make an informed choice by human beings is a right protected by Allah in Islam. In the Holy Quran He says:

“There shall be no compulsion in (acceptance of) the religion....” (Holy Quran 2.256)

Thus, there is no compulsion to take up the faith blindly and without curiosity and questioning, although Allah has shown the right path as in Surah An-Nahl He says:

“And We certainly sent into every nation a messenger (saying) worship Allah avoid Taghut” (Holy Quran 16:36).
(Taghut means false gods).

Thus, we have autonomy in the belief of God which is Himself (Allah) and we have the freedom to practice faith. For that reason, the Holy Prophet (PBH) made it obligatory for the community and the government to create the means for Allah’s followers to practice with ease and freedom. From that clear rule; scholars concluded that since people are not forced to follow the Islamic way, they should not be forced to take decisions especially when it comes to preserving their health. Their decision must be respected when they have the capacity of self-determination. This basic and important rule about human dignity has guided early Muslim scholars to think about “Autonomy” in medical research (Sachedina, 2011).

Autonomy in Islam has two essential conditions; the free will i.e. independence from the influence of others to make the decision and the ability to comprehend i.e. having the competence to independently understand and decide in order to protect one’s own interest. Based on the above argument, anyone who lacks these two conditions or at least one of them, is vulnerable and needs care of a guardian. Such cases include children, elders, prisoners, servants, people who have lost their mental ability and anyone in a similar situation.

(iv) Protection of progeny

Allah recommends Muslims to take care of their families and vulnerable members, and to protect them from any harm. Allah says:

“O’ you who believe, save yourselves and your families from the fire” (Holy Quran, 66:6).

Universal bioethical principles concur with the above that guardians are responsible for making decisions that would be in the best interest of their children when they have limited competency, so the guardian’s permission should be obtained through informed consent (Beauchamp, 2003). It is important that this permission is voluntary, given without
any persuasion or coercion, and aims to protect the well-being of the child.

(v) **Protection of property (justice)**

Earning a livelihood to support oneself, family and for the common good of the community is obligatory in Islam. As well as protecting one’s own property and wealth, is a human duty to conduct all business and commercial transactions lawfully. Allah forbids deceit and ill gains of wealth by means of misappropriation from others. Allah says:

“And do not consume one another’s wealth unjustly or send it (in bribery) to the rulers in order that (they might aid) you (to) consume a portion of the wealth of the people in sin, while you know (it is unlawful).” (Holy Quran 2:188)

Another value that is mentioned by Allah and highly enforced by His Prophet Mohammed (PBH) is Justice.

Allah spoke to His Messenger:

“My slaves, I have forbidden injustice for myself and forbade it also for you. So, avoid being unjust to one another” ("Sahih Muslim 2577 a, Book 45, Hadith 70"). Allah says:

“Adopt good behaviour and to give relatives (their due rights), and forbids shameful acts, evil deeds and oppressive attitude. He exhorts you, so that you may be mindful” (Holy Quran, 16.90).

Justice as well as equity is a requirement in Islam; for example, slaves in Islam do not carry the same obligations, neither are they liable to the same punishments as free persons because they do not have free will. Justice in medical care is the responsibility of individuals, that is both professionals and public, as well as of governments and society at large.
“And whoever oppresses (commits injustice) among you. We will make him taste great punishment” (Holy Quran 25:19).

3.2.3 Al-Ijtihad and Usul-Al-Fiqh (process and methodology in Islamic jurisprudence)

The challenges of research ethics in Islamic countries have not been widely studied. Although there is acceptance of the importance of medical research for the advancement of scientific knowledge in the new and innovative fields such as biobanks and genomics’, it is equally important to consider the religious context and to develop principles of good practice according to Islamic fatwas and Usul-Al-Fiqh.

Al Ahmad and Dierickx (2018) in their discourse emphasise that, although the Holy Quran and the Sunnah (teachings and practice of the Holy Prophet PBH) – the jurisprudence of Islam does not talk about medical research, biobanks and new developments of the present time, the process of Al-Ijtihad which means ‘to make every effort to reach the correct decision’, provides a way.

“Usul-Al-Fiqh is the methodology to arrive at decision using the Holy Quran, Sunnah and also other tools such as analogy, consensus, equitable preference, customs and public interests” (Al Ahmad and Dierickx, 2018). Islamic scholars explained that these values are applicable to individuals, families and communities. In order to apply Al-Ihsan (excellence) in the context of medical research; investigators are required to be qualified and committed to conduct the research as well as safeguard the wellbeing of the participants. The data should be accurate and transparent, and the methodology should be correct (Afifi, 2007; Rattani and Hyder, 2017). Not only that, Muslims are recommended to take into account the public interest. The general benefit of society is considered when making decisions related to a specific change or solution. In medical research, this value applies when the research questions are scientifically sound and lead to understanding, advancement or improvement of a medical issue for a
large population (Sachedina, 2011). There are other research related guidelines taken by Muslim scholars from early religious principles after extensive study and general consensus of the multidisciplinary specialists (Islamic perspectives on the principles of biomedical ethics, 2016).

3.2.4 Adab

The Arabic term Adab has numerous meanings including virtue, good behaviour and conduct, decorum, refined manners etc. Renowned scholar and theologian Hamid Al Ghazali’s (1058-1111 CE) concept of Adab focuses on Sufi literature and this discussion is centred on this genre of Adab. Al Ghazali in his Bidayat Al Hadiyat (Beginning of Guidance) advocates the duality of God-consciousness. The outward practice of Shariah rules and inner divinity (internal God-consciousness) are necessary to achieve contentment and peace, both, in this life and the hereafter.

Nesprava in his research, Human Image in Classical Islam and Sufism: Philosophical Analysis, consider the dual phenomenology of the vision of Islam, the anthropological classical direction of obligatory based approach or “externalistic paradigm” (Shariah) and the attitudinal direction of virtue based approach or “internalistic paradigm” (Sufism) (Nesprava, 2018)

Sartell and Padela (2015), propose that Islamic medical ethics should not be limited to the Shariah – obligation based ethics, but that we should concurrently, consider the discourse on Adabi – virtue based ethics. They do not suggest Adabi instead of Shariah but argue the relevance of Adab complementing Shariah ethical and moral construct.

Adab, according to Sartell and Padela (2015) is the enactment of the virtue. Thus, suggesting the ethico-legal framework of Shariah advocating the obligation to ‘do good’ and the virtuous disposition of Adab to carry out good deeds is intended to produce good results. To conceptualise, Sartell and Padela’s philosophical thought, Shariah’s
obligatory approach commands the individual to perform good, while Adab’s virtuous approach fosters godly behaviour that enhances shariah based actions.

It must be acknowledged that in almost all Muslim countries, the concept of religiosity is part and parcel of all spiritual and practical aspect of the Muslim daily life. It is also important to accept that, for progress to be made on medical research ethics. Obligatory based approach of Shariah Law remains the fundamental narrative to build the argument on the development of any guidelines. However, in Muslim countries like Pakistan, the virtue-based approach of sufistic thought Adab, is also deeply embedded into the culture, history and tradition. For that reason, it may be possible to develop a new dual phenomenological paradigm – Shariah complimented by Adab and using Ijtihad and Usul-Al-Fiqh as accepted tools to engage religious as well as academic scholars. This new paradigm, underpinned by ‘the pursuit of knowledge’ and ‘be good’ and ‘do good’ principles, predicated on Allah’s message in the Holy Quran and the teachings and practice of the Holy Prophet (PBH), may create the right environment to begin the conversation for developing ‘fit for purpose’ 21st century Islamic medical ethics guidelines.

Within medicine, there can be diverse ethical issues as there are many different health professionals involved in the care of the patients. An analysis of the limited literature available on Islamic approaches of medical ethics revealed that these challenges may occur from the Shariah or the Adab perspective ie either from the ethico-legal (Shariah – obligatory based approach) point of view or attitude and etiquette (Adab – virtue based approach). Some may argue the dichotomy of this, suggesting that there could be tensions of morality. However, it is argued that the action of the agent of ‘doing good’ is complementary to the notion of ‘for the good’ of the patient in Islamic medical ethics. In fact, it is suggested that it is equally relevant to ‘Western medical ethics discourse’ (Sartell and Padela, 2015). Al Ghazali states that by performing obligatory deeds of Shariah and voluntary acts of kindness towards others through embracing Adab may be the path to heaven. In
the context of Islamic medical ethics, it is pertinent that a Muslim physician following Shariah, through their compassionate and moral practice of medicine would enhance their God-consciousness through Adab. In his works Hya Ulum Udin (Revival of the Religious Sciences), Al Ghazali links Shariah based actions and virtuous attitudes, behaviour, and knowledge as the basis of Islamic medical ethics. Sartell and Padela suggest Adab when applied in the field of medicine instils virtue, thus providing the moral grounding for physicians to take actions in the interest of the patient and as a result provide better quality of care. Muslim history is the testament of both religious and secular knowledge being pursued in harmony. One such scholar, Ibne Sina, has written Al-Isharat on philosophy and metaphysics and Al-Aanun-Fi’t-Tibb on medicine; a book whose Latin translation was used as a text in western universities until two centuries ago. Muslims were leading in the fields of science and technology but due to the vandalism of the Mongolian invasion of Iraq prestigious libraries in Baghdad were burnt down. The revival of the 19th century did more harm when the western model was adopted, and religious sciences were separated from secular sciences (Rizvi, 1993). All teachings of Islam point towards the pursuit of knowledge and progress for the betterment and welfare of humankind. Knowledge is the basis of Islam whereby the ability to reason and to understand is given by Allah to human beings.

3.2.5 Islam and mental health

With recent national and international political events associated with Muslims and the Muslim world, there is more attention focused on their mental health, due to incidence of crime and discrimination against them (Ahmad and Reddy, 2007; Oppeldel and Reysamb, 2007; Khan and Khan, 2013). This has also given rise to increased research and publications on Muslim Mental Health (Dwairy, 2006; Ahmed and Amer, 2012; Daneshpour, 2017).
Tzeferakos G.A. et al (2017) state that in Islam, there are three spheres of explaining mental illness 1) the bio-pathological approach 2) the psychological approach and 3) the supernatural or sacred sphere. This creates the dichotomy that on the one hand, Islam places a moral obligation for the protection of the vulnerable such as the mentally ill. On the other hand, the beliefs such as being possessed ‘jinn’, ‘evil eye’ constitute the stigmatising behaviour and attitudes.

According to Keshavarzi H, et al (2020), the Islamic mental health literature can be divided into sufistic thought, biomedical model and human behaviour and beliefs. The focus of the sufistic literature is on spirituality, the methodologies of *tasfiyah* and *tazkiyah* mostly engendered in the Al-Ghazali genre. The medical model of the muslim medical doctors concentrating on diagnosis and treatment methods and the third being the model of self-management concerning with the human behaviour and attempting to look at one’s own self convictions with rational and reasonable perspectives to change for the better. Keshavarzi H, et al refer to this genre as ‘Ethics’. A systematic review by Koenig H.G. et al (2019) established that the pillars of Islam such as praying five times a day, fasting in the month of Ramadan and performing the rituals of Hajj provides structure of self-discipline and promotion of mental health and wellbeing. They concluded that muslims who practice these actions coped better with stress and anxiety than those who did not. Baasher T.A. (2001) concur that this strategic intent in Islam sets direction and provides guiding principles for good mental health and wellbeing.

3.3 Case Study

The current case study is self-harm and suicide prevention in adolescents in the context of Pakistan. It is a multi-centre RCT to evaluate the clinical and cost effectiveness of a culturally adapted manual assisted psychological intervention (YCMAP) plus treatment as usual (TAU), as compared to treatment as usual in Pakistani adolescents with a history (within 3 months) of self-harm. In the context
of this study, self-harm is defined as: “an act with non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without interventions from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognised therapeutic dosage, and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences” (Platts et al, 1992)

The programme of research follows a Medical Research Council (MRC) funded culturally adapted Manual Assisted brief psychological intervention (C-MAP) trial in an adult population to determine the clinical effectiveness over one year of CMAP. Therefore, it provides a perfect opportunity to study how the above issues in research ethics are applicable in a related trial; to evaluate the intervention on a younger population, the YCMAP study (also funded by the UK National Institute of Health Research (NIHR and MRC).

Being a multi-centre design and having a series of studies in varying populations and contexts, it provides a valuable opportunity to assess the ethics of RCTs as a whole programme of study where evidence accumulates until it becomes overwhelming or ‘definitive’.

The target population is all patients of age 12-18 years presenting to the participating general practitioners (GPs) and emergency departments, admitted to the participating hospitals after an episode of self-harm, or self-referrals. Patients meeting inclusion criteria are invited to take part in the study by the GP, ward or emergency department doctor who makes the initial assessment.

### 3.3.1 Inclusion Criteria

- Age: 12-18 years.
- History of recent self-harm which is defined as “self-harm occurring within the last 3 months (from the initial identification of a potential participant)”. This period is considered as high risk for repetition in young people (Hawton K, et al 2012).
3.3.2 Exclusion Criteria

- Patients with a severe mental illness, such as psychotic disorder.
- Patients with conditions limiting engagement with assessment/intervention.
- Temporary resident unlikely to be available for follow up.

Over 700,000 people die by suicide each year and 77% of these deaths occurring in LMIC (WHO, 2021) such as Pakistan. Suicidal behaviour remains an under-researched and under-studied subject in Pakistan and there is no official data available (Khan et al., 2006; Abidi et al., 2010). The limited evidence calls for more robust research designs, along with a focus on risk factors (Shekhani et al., 2018). Suicide is the fourth leading cause of death in 15-19 years old (WHO, 2021). Self-harm is a major risk factor for eventual suicide, and the prevention of self-harm is therefore a key focus for suicide prevention efforts (Hawton et al., 2007; 2015). Young people are especially at risk of suicide and self-harm (WHO, 2014). For example, the prevalence of self-harm over three months in young people in India was 3.9% to 25.4%\(^1\) (Aggarwal, 2015; Aggarwal and Berke, 2015). This might be due to the fact that half of all mental health conditions start by 14 years of age but most cases are undetected and untreated (Kessler et al., 2007). Moreover, risk-taking behaviour is prevalent in adolescence, this can be both an unhelpful strategy to cope with poor mental health and can severely impact mental and physical well-being (WHO, 2020). As such young people with a history of self-harm are a priority group for interventions. Some of the common problems experienced by the youth in Pakistan are unemployment. International Labour Organisation put the unemployment for 15-24 age group at 10.8 % in Pakistan. Violence

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\(^1\) Wide range may denote uncertainty of scale
and trauma survey with 320 students; 93% reported having lifetime exposure to at least one traumatic event, cyber harassment; 26% children aged 8 – 17 reported cyber harassment (survey conducted by Telecommunications Research Group for Microsoft Corporation), bullying (In a survey with 4600 adolescents; 41% reported being bullied in last 1 month. Ministry of health 2009) and early child bearing; 21% women married by the age of 18 (Pakistan UNICEF 2018)). It is to be noted that 11% (13 million) of all births are given by girls aged 15 to 19 years; 95% of these occur in LMIC (WHO 2016), and that the world’s second highest rate of adolescent pregnancies occurs in South Asia with the highest birth rate in Bangladesh (113), followed by Nepal (71), Afghanistan (51.9), Pakistan (44), Bhutan (28.4), and Sri Lanka (20.3);

A recent scoping review by Shekhani et al. (2018), synthesised literature on self-harm in Pakistan, highlighting the characteristics of this population. Self-harm was more frequent in females of a younger age group. Unemployment was associated with self-harm, but this varied across studies. Self-poisoning with insecticides and pesticides was found to be the most common method in both urban and rural areas. The review identified a gap in evidence exploring clinical characteristics of self-harm in Pakistan (Shekhani et al., 2018).

A systematic review of talking therapies in adolescents, an updated Cochrane review (Hawton et al., 2015) on psychosocial and pharmacological interventions for prevention of self-harm in children and adolescents have also been completed: The aim of the review was to identify any trials published from LMICs. Results of the study showed no trials published on psychosocial and pharmacological interventions for prevention of self-harm in children and adolescents from LMICs. A search on google scholar by myself, the researcher using "Adolescents AND Self-harm AND Cognitive behaviour therapy AND LMIC resulted in one systematic review, Psycho social interventions for self-harm in low-income and middle-income countries": systematic review and theory of change (2021). In the SR,
only one study with adolescents SH (12-18) was coded, Effectiveness of Cognitive-Behavioural Therapy in Decreasing Suicidal Ideation and Hopelessness of the Adolescents with Previous Suicidal Attempts in which they collected data from 2011-2012.

There is however, evidence from developed countries that psychological therapies, including those based upon Cognitive Behavioural Therapy (CBT) principles, can help prevent further self-harm in those at risk, including in young people (Hawton et al., 2015; 2016). Although, this evidence is limited and to a great extent, from western and HICs. Considering the elevated and potentially increasing suicide rate in Pakistan (Shahid and Hyder, 2008), therapies for self-harm in young people are vitally needed in this country. Therapies that work in western countries cannot be implemented in their current form due to cultural, religious and social difference such as customs and traditions, collectivist cultures and different religious belief systems (Memon et al 2021) but need to be adapted to account for cultural differences (e.g. differences in the understanding of mental health and problems like self-harm). Pakistan is a challenging context to evaluate new treatments in. Self-harm remains a criminal act and mental health resources are limited. Despite this, the research group conducting the study ‘A Youth Culturally adapted Manual Assisted Psychological therapy (YCMAP) for adolescent Pakistani patients with a recent history of self-harm’ has successfully conducted a trial of a psychological, culturally-adapted therapy for self-harm in adults in Pakistan (the CMAP trials; Husain et al., 2014). The CMAP intervention draws on CBT principles but has been adapted for the specific cultural context of Pakistan. A version of CMAP has been developed aimed at adolescents (YCMAP) adapted from Cutting Down – A CBT Workbook for young people who self-harm (Taylor, Simic and Schimdt, 2015).

3.3.3 YCMAP Adaptation Process

The YCMAP has been adapted with permission from a self-help guide called “Life After Self-Harm” and “Cutting down: A CBT workbook for
treating young people who self-harm" (Taylor, Simic and Schimdt, 2015).

The process of cultural adaptation of the YCMAP manual took place in Pakistan and was guided by two trained therapists and supervisors (senior researchers at PILL, Dr Zainab Zadeh (ZZ) and Ms Tayyeba Kiran (TK)). Discussion rounds were done in which the English manual was read in groups to get familiarised with the content, to highlight things that needed to be adapted, and discussed evidence-based suggestions for this population, with respect to content and structure of the intervention. A standardised protocol (Rahman, et al, 2003) was followed for the cultural adaptation of the manual which include the following steps.

1 Team composition: The adaptation team comprised of therapists, translators, supervisors, and service users who had command of both English and Urdu language.

2 Translation: After discussions, the manual was assigned to an artist, Uzma Omer (UO) for cultural adaptation of pictures and also to the manual club team for translation based on these three levels:
   a. Linguistic or Semantic Level: To keep translated meaning as near as possible to the original meaning. Difficult words were discussed within the team, and then run with service users (adolescents, parents) to make it more meaningful and understandable.
   b. Technical Level: The focus was on the technical aspects of language such as grammar, tenses, exercises/session activities/tasks, characters names, and their relationship to the sociocultural context. For example, character names were changed so that participants could easily relate to themselves.
   c. Conceptual Level: In order to make it more appropriate to the cultural context, it was made sure to use words that related to Pakistani culture.

After translation and proof reading, the manual was presented to service users, and therapists for feedback.
As part of the internal pilot phase, the manual was reviewed again in a small team (ZZ, TK and Sehrish Tofique (ST) (Lead researcher YCMAP)). Written feedback on each session from all therapists, who delivered YCMAP session was incorporated in the manual. This related to the use of simpler language and modern-day slangs, familiar to the youth. Based on their feedback, instructions for the therapists and completed exercise sheets were added as a template for more understanding and clarity for the participants, as well as the therapists.

The current study will use an RCT design whereby young people with a history of self-harm are randomly assigned to either receive TAU, or TAU plus the YCMAP intervention.

Since the benefits of YCMAP are unknown it is methodologically most efficient that participants are randomised to groups in this way, to ascertain whether according to traditional standards of evidence-base medicine, the therapy is helpful.

The primary aim of the RCT is to determine the clinical effectiveness over 12 months of the YCMAP. The primary outcome is repetition of self-harm 12 months after participants are randomised to YCMAP plus TAU or TAU. Secondary outcomes include suicidal thinking, hopelessness, distress and quality of life, all variables known to be related to suicide risk. In Pakistan over 36.01% of the population is 0-14 years of age (and around 19.3% of the population is between the ages of 15-24 years (CIA World fact-book, 2020).

According to Lilford et al (2001), appropriately executed RCTs are generally accepted to be the most dependable approach for comparing health technologies and equipoise as the state of epistemic uncertainty is traditionally regarded as both the necessary and sufficient ethical condition stipulated by regulators such as Food and Drug Administration (FDA) Agency and National Institute of Clinical Excellence (NICE) to justify randomisation in clinical trials. However, there is little literature on its potential role in justifying randomisation
within two arms where the intervention has been shown to work in a different study population (to test the generalisability of the original results) and where the intervention is psychological plus TAU vs TAU which can include drug therapy. This research will examine the main conceptions raised by multi centred randomised trials, especially to evaluate pharmaceutical or psychological interventions as in the YCMAP programme. In particular, as CMAP trial has already yielded results, the limits to the level of epistemic uncertainty needed to justify further trials will be investigated.

Conversely, there is little agreement over how much evidence is sufficient to change practice or to make policy decisions. The traditional approach to evidence simply applies standards of evidence used in the regulation of new medicinal products to other cases. However, these standards may be inappropriate for making decisions about health service funding and regarding individual patients in clinical practice where individual preferences and value trade-offs must be made, for example NICE guidelines recommendations.

3.4 Right to Health

Having discussed the conceptual basis of equipoise as the moral justification for conducting RCTs in Chapter 2. Our debate now moves towards the ethical considerations regarding clinical trials and human right law. Furthermore, in the context of this discussion, we examine the ethical basis pertaining to YCMAP trial and the trial’s compatibility with a legal right to health given access to the intervention was restricted to the RCT despite their being some data on efficacy of the intervention and treatment preferences, albeit in different populations namely adults in Pakistan and CBT based research in young people in Western countries.

In this segment, I will i) review a landmark legal case under human rights law in South Africa, ii) show why this legal case is relevant to human right to health more generally, iii) review ethical theory behind
human right to health, iv) show that mental health is covered by human right to health, v) show why Y-CMAP is scientifically justified despite CMAP and evidence from other CBT based therapies for children in Western countries, vi) show the factors affecting right to access intervention outside research in legal case not apply in YCMAP, and finally vii) show how YCMAP contributes to wider effort to realise human rights in Pakistan,

**Introduction**

Right to health is a basic human right. The World Health Organisation (WHO) Constitution 1946 defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. It goes on to state that “the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.” Article 25 of the Universal Declaration of Human Rights 1948, refer to health and well-being as part of ‘adequate standard of living’ and the 1966 International Covenant on Economic, Social and Cultural Rights makes it incumbent on the States to adhere to human rights including right to health of their citizens. There are other treaties and declarations internationally that place an obligation on governments to abide by the citizens’ human rights such as right to health and healthcare which is medically and scientifically congruous. Furthermore, there is commitment from the States under the United Nations Charter to observe and promote human rights. Our discourse further on in the chapter will converse about the philosophical notions of health and provide an update on WHO definitions on right to health. However firstly, I will provide a critique of the South African prohibition to roll out access to an intervention which had prior evidence base within the country as well as elsewhere. It is relevant to have this discussion in comparison to my case study YCMAP, as this intervention had been already tested in Pakistan, albeit in adults and resulted in improved outcomes. Nevertheless, the South African
intervention required government funding while YCMAP is funded by MRC, UK.

### 3.4.1 Case law: Children’s legal right to access intervention.

The main challenge to testing generalisability of RCTs by running further RCTs is the landmark ruling in *Treatment Action Campaign and Others v Minister of South Africa and Others*. This case was resolved in 2002 by the South African Constitutional Court which is the highest court in the country for such issues. The case was against the South African government for their refusal of the provision of drugs to HIV positive pregnant women to stop the transmission of virus to the child (Bailey, 2006). South African health authority disagreed to quickly expand access from the pilot sites, the prescribing of Nevirapine to expectant mothers to prevent transmission of HIV to their babies. This was the only intervention available and the evidence from RCTs done elsewhere was that Nevirapine significantly reduced transmission on which basis the South African government established a protocol. The Protocol for Providing a Comprehensive Package of Care for the Prevention of Mother to Child Transmission (MTCT) of HIV in South Africa. Following this, two sites were set up in each province and Nevirapine along with breast milk substitute and counselling was offered to HIV infected mothers. The South African government decided that it would monitor the pilot sites for two years in order to understand the financial and logistic implications before considering scaling up the provision across the whole country. However, Nevirapine was already being prescribed privately and the Medicines Control Council (MCC) formally licensed Nevirapine for prevention of MTCT in South Africa. The pharmaceutical company had agreed to provide free supply for five years. The lawsuit was based on children’s special rights to health according to the South African Bill of Rights which in Section 28 states, “Every child has the right — (c) to basic nutrition, shelter, basic health care services and social services’ [18].
The Convention of the Rights of the Child and the International Covenant on Economic, Social, and Cultural Rights were also cited to support this interpretation of children’s right to health [14,19].” The court ruled in favour of the Treatment Action Campaign on the basis that benefits of Nevirapine outweighed the harm significantly. The decision of the High Court “determined that the government had breached both the negative obligation not to interfere with the realization of health, and the positive obligation to provide a comprehensive and systematic plan to progressively realize the right to health” (Bailey 2006). The health authority appealed that the responsibility lay with the parents. However, the court deemed it to be a right to health obligation of the government not to interfere with free supply of a ‘proven’ intervention despite the government’s concerns about local circumstances which could affect its implementation.

On the face of it, MTCT seems like a violation of child’s right to health and this is also how it is seen by legislators and courts (Bailey, 2006). Nonetheless, it is underpinned by notable concerns about women’s right towards their reproductive health and access to healthcare. Furthermore, according to Bailey, her right to be informed, her right to have children and access to equal treatment.

In the past involving children in clinical trials was deemed unethical. However, now due to innate physiological differences between children and adults, they are considered necessary (Bwakura-Dangarembizi et al, 2012). Developing countries carry a high burden of disease in children due to environmental, malnutrition due to poverty and poor sanitary conditions. Arguably, this warrants urgent moral obligation and special protection under their right to healthcare and research. Odowu and Edwards (2014) in their systematic review highlight, from their interpretation of international documents, three types of obligations on the States; “the duty to respect, protect and fulfil human rights. This interpretation in clinical trials is any denial or restricted access to healthcare by the State is against the duty of respect. Duty to protect is to give equal access to healthcare and health care services and also to
ensure any third party is obliged to do so. Lastly, the fulfilment of the obligation is the provision of healthcare and healthcare services by progressive realisation through legislative, political and health care policy.

3.4.2 Relevance of case to human rights law more generally.

As stated by the UN, there is a human right to health which includes access to healthcare, health services, clean water, food, proper housing and sanitation. It is also a basic human right to refuse medical treatment. The signatory nations on the UN Charter are legally obliged to provide a health care system for their citizens which cater for prevention, management and treatment to control disease. For decades, successive international legal and moral instruments have promoted the right to health but this right varies from country to country depending on the economic, social and political environment of the country. As science has advanced over the years and with the advent of high technological treatments, people are living for much longer. Consequently, with the aging population there are more co-morbidities requiring expensive interventions and medicines. Resourcing adequate healthcare is becoming more and more challenging in HIC let alone in LMICs. Inevitably, cost effectiveness has become a major factor in making healthcare decisions. This brings about ethical and moral challenges when resources are insufficient to match demand. At the same time as there is an obligation on governments to comply with their citizens’ basic right to health, within that obligation there is also a mandate for States to progress new developments in the interest of preserving the health of the nation. Research plays a pivotal role in the pursuit of new knowledge and development of new medicines and intervention for the benefit of the society at large.

Historically, research in the interest of benefitting the whole society has also been at the cost of harming marginalised communities. Research involving human subjects has propagated unethical and at time
criminal practices. Several international legal and ethical codes and moral instruments have been established such as the Nuremberg Code, following the atrocities carried out by Nazi doctors and the Declaration of Helsinki by the WMA as a consequence of the Tuskegee trial and other unethical practices towards human participants of clinical trials. These efforts have been in the pursuit of protecting the human rights guided by the bioethical principles of beneficence, non-maleficence, autonomy, and justice. There is vast literature available on the ethical issues that may arise when conducting clinical trials namely around recruitment, on how informed is ‘informed consent’? or conflict of interest.

Children have special rights to health due to their vulnerability due to age and their dependence on adults on consent giving. In LMICs where there is a higher burden of disease affecting children and therefore more research takes place on child health issues, there is the likelihood that it exposes them to potential risks around ethical challenges. Another vulnerable group is mentally diverse persons, their human rights in general and their right to health can be further eroded due to cultural and social beliefs around mental illness. Discrimination and stigma due to the cultural and societal attitudes and misunderstanding can seep into education and health systems which in turn marginalise their employment opportunities and earning potential. Therefore, research studies such as YCMAP is the right step towards addressing the urgent need, to develop more evidence base to fill the gap in this under developed area of research in LMIC.

As our case study, YCMAP trial is based in Pakistan, it is important to set the frame of reference of health care and healthcare services provision in Pakistan.

European Commission Medical Country of Origin (MedCOI), 2020 noted that Pakistan is ranked 154 among 195 countries in terms of access and quality of healthcare. The Sehat Sahulat Programme was launched by the previous prime minister. This model of care is built to
align with the UN UHC and the SDG agenda by 2030. However, currently healthcare and facilities are hugely lacking with respect to the population that it needs to cater for. According to WHO Regional Office for the Eastern Mediterranean (EMBRO), Pakistan Health Service Delivery, there are a total of 1,279 hospitals, 5,671 dispensaries, 747 maternal and child healthcare centres, 441 tuberculosis centres, 686 rural health centres, 263 sub-health clinics and 5,264 basic health centres across Pakistan in 2018, with a combined total of 132,227 beds. The WHO Mental Health Atlas (2017) profile for Pakistan reports that there are 11 psychiatric hospitals in the country, 800 psychiatric units and 578 residential care facilities offering inpatient care. According to the WHO report there are 3,729 outpatient mental health facilities, out of which there are only 3 for children and adolescents. There are 400 psychiatrists and most of them work in urban areas. The 2020 report also stated that mental health problems are a taboo and people did not reveal mental illness. The report alleged

“In Pakistani culture, it is commonplace to approach spiritual or traditional healers in cases of physical and mental illnesses. Faith healing is the traditional way of treatment for mental ailments in this culture, as people usually perceive mental illness to be the result of supernatural influences. Use of faith healers is irrespective of socio-economic factors as it usually depends on the person’s belief toward spiritual healing. Faith healers are a source of care for people with mental problems in Pakistan, particularly for women and those with little education.”

As stated elsewhere in my thesis, self-harm and suicide is a criminal act in Pakistan. The Mental Health Ordinance was enacted in 2001. However, only three Pakistani provinces have mental health rules in place.

In the context of the above statistics and considering Odowu and Edwards 3 types of obligations on the government towards the duty of right to health by respecting access to health, protection by making
healthcare available and fulfilment towards the right to health. The Sehat Sahulat Programme in Pakistan is progressing to realise right to healthcare but as revealed from the YCMAP Theory of Change stakeholder workshop, there may be no treatment as usual for self-harm and attempted suicide in adolescents in Pakistan. Research trials like YCMAP may be the only way treatment would be available for young people. Findings from the YCMAP trial on the effectiveness of the intervention will provide evidence based treatment for self-harm, to crucially meet the clinical need and to help inform policy on self-harm in children and adolescents. Thus contributing towards the wider effort of progressive realisation of right to health for children in Pakistan. However, a pertinent point to raise here is although UN’s global health agenda is UHC but unfortunately this has the risk of remaining a rhetoric as only 0.2% of WHO research funding goes to LMICs.

3.4.3 Ethical theory behind human right to health

John Rawls in his Theory of Justice argues that the two basic principles of justice are Liberty and Equality (Rawls, 1971). It could be assumed that the right to access to health care is a social good that can come under the principle of equality as suggested by Norman Daniels. The discourse above establishes that the rhetoric of right to health is enshrined legally and morally in covenants and treaties and in order to protect health, it necessitates fair availability of medical services, protections of health and a fair distribution of social determinants of health (Daniel et al 2000). With regards to the right to health care, the remit varies from country to country dependent on the health care system. With the advent of new technologies and high costs of advance therapies, cost efficiency plays a big role in setting the threshold on a right to health care. This brings about discussions on the morality and societal obligations on provision of medical services and the ambit of right to health care. The justification of this utilitarian approach is that health system resources are finite and accommodate the greater good of the society (Mandal et al, 2016). Various theorists have sought to ground the right to health care under principles of
justice. Daniels, 1985 propose a right to health as a right to equality of opportunity based on Rawls's (1971) Theory of Justice, underpinning the issue of health care with Rawls’s notion of fairness, since the theory highlights a principle protecting equality of opportunity (Rawls, 1993). Philosophical theories try to define health as ‘normal’ physical functioning, capability or positive experiences, for example Christopher Boorse’s bio-statistical model (Boorse, 1997). However, Kingma 2007, pulls apart Boorse’s Bio-statistical Theory (BST) which is based on reference classes of “‘health’ as the statistical normal functioning and ‘health’ and ‘disease’ as empirical, objective and value free concepts” (Kingma 2007). BST does not take into account other concepts of severity and sufficiency such as downs’ syndrome or too much testosterone in women is classed as disease although healthy in men. As well as the concepts of social disapproval and disease such as mental illness and sexuality. Kingma concurs that by using other reference classes, we would arrive at different accounts of health.

3.4.4 Governments Duties to Support Research and Development

Right to health confers positive obligation on States to promote the development of new drugs, vaccines and diagnostic tools through innovation and development and through international cooperation. Article 32 of the Convention on the Rights of Persons with Disabilities (CRPD) state “Facilitating cooperation in research and access to scientific and technical knowledge” (https://www.un.org › development › desa › disabilities)

Interestingly, there is acceptability with respect to medical ethics, cultural and gender sensitivity. Also, it is all well and good to assert the obligations of governments on right to health of their subjects. However, on the other hand, it will be prudent and realistic to acknowledge that not all these rights will be possible to be honoured at once particularly by low resource countries. This, WHO and the UN accepts and the Covenant deems it to be ‘Subject to progressive
'realisation'. According to Brolen et al, 2017, a country’s fundamental duty under ‘progressively realise’ is rights for all citizens and in particular vulnerable ones. They state that the Covenant distinctly advocate that the attainment of this right is reliant on shared responsibility between HICs and LMICs and other agencies for implementation. Consequently, it becomes critical for high resourced countries to assist and work in partnership with other States so that they can fulfil their duty to the right to health. Nevertheless, all states should undertake every endeavour to meet their commitment towards their citizens’ right to health.

International collaboration in research is increasingly important in tackling common and infectious diseases which cross national boundaries. Globalised research initiatives are helping build capacity and capability worldwide such as the WHO’s Global Observatory on Health Research and Development. The Observatory is a source of information and health analysis on human diseases. It provides knowledge for monitoring and decision making on health Research and Development (R&D) gaps as well as highlights priorities for new investment and capacity and capability building needs. According to the WHO Global Observatory on Health R&D, international funders awarded only 0.2% of grants to LMICs.

(https://www.who.int/observatories/global-observatory-on-health-research-and-development)

There are also philanthropic organisations, Non-Governmental Organisations (NGOs) and public/private partnerships such as initiatives in partnership with pharmaceuticals, working in international cooperation to develop and innovate in science and technology in order to promote health and health care. The WHO in its role of convenor has R&D blue print teams that have developed R&D road maps, which provide frameworks for benchmarking and monitoring of new innovations, research, and experiments on methods such as clinical trials for healthcare, cluster trials for community interventions, assessments for policies etc.
The increasing reliance on public-private partnerships such as with pharmaceutical companies warrants international standards and regulatory guidelines to protect human subject participating in research. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human (ICH) Use was set up in 1990 to bring together regulating authorities and pharmaceutical companies to develop ICH guidelines in order to ensure safety, effectiveness and quality of new medicines that are developed and that there are shared national standards for clinical trials of investigational medicinal products. Pharmaceutical industries and regulators have equal stake. Currently, revisions to E7 (R3) is in process to increase methods with the aim to make the guidelines culturally sensitive and more globally relevant (https://www.ich.org).

In the wake of the Covid 19 pandemic, the Organisation of Economic Co-operation and Development (OECD) advocate determined support by HICs towards developing countries in an effort to prevent further loss of life and provide assistance, in order to build resilience and sustainable recovery. OECD propose that some of this support can be in the development of the healthcare sector, global efforts of debt management and subsidised resource allocation as well as a shared agenda to design a green and sustainable recovery model. (OECD 2020)

3.4.5 Mental Health covered by Human Right to Health

The UN Human Rights Convention report states that the right to health grants the individual from the health system the same rights of acceptability, accessibility, availability and quality of health services in the context of mental health. Article 12 proclaims that “Mental health is not merely a health or medical concern, it is very much a matter of human rights, dignity and social justice”. (Article 12, UN Convention on the Rights of Persons and Disabilities (CRPD)). Amon et al, 2022 differentiate discrimination from stigma stating discrimination and stigma is often lumped together by scholars. Discrimination is a blatant
abuse of human rights and is separate from stigma which is more about experience and practice. According to Article 12, CRPD States have legal obligations towards the right holders’ entitlement to physical and mental health and well-being. The Office of High Commission for Human Rights (OHCHR) report (2017) on mental health and human rights recommends a human rights based approach to mental health. The Covid 19 pandemic has intensified the need for States to take urgent measures for mental health based on human rights. It is widely acknowledged that the pandemic has had a detrimental impact on the health and well-being of the population at large. Furthermore, it has impacted negatively on people with mental health and psychosocial difficulties more disproportionately as well as those more vulnerable such as the older population. According to the UN, the pandemic has impacted progress on the 2030 agenda of UN SDGs, in particular SDG 3 which is to ensure health and well-being and SDG 10 to reduce inequality, both within and between nations (OHCHR, 2017). Although most nations have signed the Convention on the Rights of Persons with Disability, there is a need for rights based legislation on mental health and other vulnerabilities to ensure compliance with the Convention on mental health related areas.

The UN Human Rights Council defines mental health as “a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community” (Mental Health and Human Rights, 2017) and for young people and children “the capacity to achieve and maintain optimal psychological functioning and well-being”. According to the UN report, the social and economic determinants to health impacts on the individuals’ mental health and well-being, poverty, poor housing and lack of education being significant contributing factors. Stigma and stereotyping due to social and cultural pigeonholing are major barriers, this in return impact on the persons’ agency and self-esteem. Consequently, not doing well in the education system. This spirals into a vicious circle of lack of
education resulting in poor employment and hence societal inequalities detrimental to physical and mental health and well-being. In cultures such as Pakistan, the negative beliefs towards mental illness as someone being ‘possessed by the devil’ propagates discrimination and stigma. These cultural attitudes can infiltrate into education, healthcare and work place settings and create further barriers towards equal human rights. In Pakistan, the Mental Health Ordinance 2001 replaced the Lunacy Act 1912, since then most acts have been at provincial level (Khan, 2021). Although the guidelines from the Lunacy Act 1912 on basic human rights of the mentally ill continue to hold such as confidentiality, consent and appropriate treatment on attempted suicide. According to Khan et al. the lack of national legal accountability towards mental health has been challenging and suicide remains a criminal act to this day. In February 2018, an amendment to the Mental Health Ordinance 2001 to decriminalise attempted suicide was proposed but it still needs implementation. Most challenging is the application of blasphemy laws in Pakistan with the mental health law. Time and time again, Blasphemy Law has been used to victimise minorities and people with disabilities such as Down’s Syndrome. (Husain, 2014). Societal stigma due to lack of awareness of mental illness persists in Pakistan. This lack of understanding on the legal front as well as religious misconceptions remains a hindrance to the utility of the scarce infrastructure that exists.

3.4.6 Why restricting intervention to RCT scientifically justified in Y-CMAP

According to Mcgorry, mental health services have traditionally focussed on adults. Although, evidence shows that 75% of mental illnesses occur before the age of 25 years. Generally, services for adolescents are poorly organised as the focus until recently has been split between adults and paediatrics (Mcgorry, 2018). According to Collizi et al, the theoretical rationale for intervening at this age in terms of mental health is firstly, mental health is the crucial element for a
person to function physically and socially as well as to be able to cope with life events (WHO, 2013). Secondly, most incidences of mental illness occur before the age of 25 (Kessler, et al, 2005) and thirdly, as mentioned most traditional mental health services have proven to be ineffective in this vital stage of life (Andrews, et al, 2000). This evidence suggests that there is an urgent need to develop early intervention strategies for young population.

The Consolidated Standards of Reporting Trials (CONSORT) advocate that Evidence Based Research (EBR) is essentially predicating the new study on the prior knowledge and results of previous validated research (Robinson, 2007). According to Chalmers et al, 2002, although cumulative scientific knowledge adds rigour, it is rare that scientists cumulate evidence in a systematic manner. Chalmers et al reiterate the importance of informing new studies with existing evidence. By underpinning the new study with existing knowledge provides legitimacy and adds value. (Altman et al, 2001). Our case study, YCMAP is built on the evidence base of a previous study CMAP for adults and some elements of CMAP were beneficial for young people. However, CMAP is not externally valid in young people. Woolcock, 2013, state “we have compelling empirical evidence that inferring external validity to given empirical results – i.e. generalizing findings from one group, place, implementation modality or scale of operation to another – is a highly fraught exercise”.

Lieder et al, in their study of social learning concluded that children and adults use different strategies. Howard 1913, infer there are differences in adults and children in the learning process, memory, attention span, ideation, responsiveness to suggestions and reasoning.

Young people are different from adult, when doing research, we cannot depend on what we know from research from adults (Idler, 2013). According to Idler, there are five key differences between children and adults that we need to consider when conducting research.
1. Physical development: Adults are not growing anymore so their height, strength and hand size remains consistent. On the other hand, children and young people are not as developed as adults and can differ vastly by age. They also have limited eye-hand coordination.

2. Cognitive development: Cognitive abilities in children and young people are still developing. Whilst, generally speaking adults have similar mental abilities which means they can communicate in a natural way. Children and young people have differing cognitive abilities. Small children are very egocentric and perceive everyone sees the world as they do. As they grow older and learn new things their thinking becomes more abstract and they begin to consider other perspectives.

3. Social Development: Adults have learned social rules and values such as empathy and to treat others the way they would want to be treated. Children can be very self-centred. They give preference to their own needs and interests above those of others. As they get older, this perception of self-changes and they learn to be empathetic, relationship to others change and they develop their own personality with individual character traits and personal preferences.

4. Concentration: Adults respond well to incentives and once committed generally stay consistent. Young people are very spontaneous, excitable and easily distracted and their concentration span is limited.

5. Experience: Children and young people have less experience. Adults have a life time of experience and can generally learn to apply their experience from one situation onto others. As young people have less experience, it is important to give them sufficient information as less foreknowledge can cause uncertainty and discourage them to participate in research.

Interventions for adults are often more of a historical interest and maybe focused on helping the person to get insight and achieve understanding (Kendall, 2011)
Bogin, 2015 study of evolution of human growth and development characterise that adolescence is a peak time of risk taking behaviour, both of mind and body and that psychiatric and behavioural disorders often occur in adolescence.

“correcting faulty information processing (ie changing distorted thinking) and/or teaching strategies to overcome a deficiency in information processing (ie overcoming deficiencies in thinking) are both valuable steps in the treatment of psychological disorders of youth” (Kendall, 1993).

Talking therapies for young people are directed by theories that address psychological change in youth and focus on human development due to their emotions, behaviour and emotional problems related to youth (Silverman & Hinshaw, 2008). Young people face different developmental issues and their ability to accept and manage their emotions are not fully developed. Gardner et al, 2013, infer that interventions designed for children and young people are conceived on the background of developmental changes and various levels of interactions of social influences on the child requiring outcome measures based on psychopathology, co-morbidities as well as family functioning and child wellbeing.

Schenk and Williamson, 2005 argue that children and adolescents may come to harm due to less power and availability of resources as compared to adults. Consequently, it is challenging and problematic to use on children the same strategies of collecting information from adults, without putting additional safeguards to address special needs of young people.

Two young delegates at the UN Special Session on Children 2002 proclaimed “We want a world fit for children, because a world fit for us is a world fit for everyone”.

Bell, 2008 deduce that research guidelines specifically for children tend to omit directly referring to human rights principles as articulated in UN Convention of Rights of the Child (UNCRC). As more research is taking
place with children actively involved as research participants, Bell advocates a human rights approach and propose that researchers should comply with their obligation to promote and protect human rights of children and research ethics guidelines should be informed by the principles of UNCRC. Bell argues that UN Special Session on Children 2002, highlighted the need for society to focus on human rights, in particular the right of children to participate in decision making in all matters concerning the right of the child. There is likelihood that researchers, like all adults may ignore children’s views but children are moral agents and social actors in their own right (Alderson and Morrow, 2004, Hill, 2005). Children are not small adults; they have an additional, unique set of interests (McIntosh 2000, p. 177).

**YCMAP**: comprises of 8-10 sessions delivered over three months. The first eight sessions are offered weekly and further sessions fortnightly on a one-to-one basis and each session lasts for about 60 minutes. The YCMAP has been culturally adapted with permission from “CMap” (Husain et al, 2014), “Life after self-harm” (Schmidt & Davidson, 2004) and “Cutting down: A CBT workbook for treating young people who self-harm”(Colucci,2015). The intervention includes psychoeducation and a comprehensive cognitive behavioural assessment of the self-harm attempt using virtual stories of four young people. The therapy focuses on current problems that contributed to the self-harm episode. Therapists and adolescent clients choose from a list of techniques those which are most relevant to the client’s problems. Therapy is therefore adapted to fit with the clients’ problems and primarily utilises problem solving, CBT, and dialectical therapy strategies to bring about change.

To help determine the most appropriate coping strategy, a coping tree is designed. Training in assertiveness and anger management are offered to help the young person to develop resilience to cope with stress. To the existing YCMAP, we will also aim to review the look and feel of the resource by including licenced content from My Big Life - a course developed by our collaborative partner Five Areas Limited. This accessible, story-based approach uses illustrations of young people
facing different scenarios at home and at school to illustrate key CBT-based concepts: Understanding your feelings - How to get a Big Life (behavioural activation) - Thinking in a Big Life way (identifying and changing thoughts that upset and affect how you feel) - Relaxation approaches - Building inner confidence - Practice scenarios - Trainer notes and linked worksheets/prompt cards and posters. Asian versions of the course already exist with amended artwork. As part of the development programme, selected content will be added to the course and trainer notes will be modified (based on feedback from participants) as needed.

As adolescents were excluded from the original CMAP study, the above justification provides an ethical imperative to conduct YCMAP.

Young people as key stakeholders in our Theory of Change workshop helped with the design of the protocol. The trial will not only test the intervention in the YCMAP arm but will also conduct assessments at 3, 6, 9 and 12 months in the control group, following randomisation. Thus facilitating access to healthcare to all. The above discourse highlights the importance for the need to conduct the RCT (YCMAP) in order to determine the efficacy of the intervention in adolescents and to generate new evidence base which may potentially be generalised in LMIC. The above argument from the right to health perspective, provides the rationale for restricting the intervention is scientifically justified and that CMAP is not externally valid in young people. It is also relevant to point out that the funding from MRC was specifically for the purpose of conducting the trial to establish whether it improves outcomes and is cost effective.

3.4.7 Intervention not offered free to all but only part of RCT funded by external UK MRC
On the backdrop of the discussion above, it is relevant to point out that although YCMAP would certainly assist the Pakistan government in fulfilling its obligations towards progressive realisation to right to health, it is not pretending to resolve the issue of full-scale access to mental health services in Pakistan, which is the responsibility of the State. YCMAP is very different from the South African case debated in the beginning of the chapter. The intervention (YCMAP) is not publicly funded by the Pakistan taxpayer or offered free of charge by the funder (MRC) to all eligible patients. Hence, the conditions are very different from the legal case in South Africa. Notwithstanding, YCMAP trial will facilitate access to mental healthcare in Pakistan.

The above ethical analysis of principles and regulations on right to health and healthcare reiterate the moral and legal obligations of governments towards their citizens. With innovation and the high cost of new technologies, it is also an ethical and moral duty towards the taxpayers that resources are spent on health care services, which are good quality and deliver value for money. According to Vergel et al, 2008, health systems such as in the UK now require new technology producers (pharmaceuticals) to demonstrate cost effectiveness before funding them. The Department of Health in the UK has outsourced to NICE, an independent organisation to appraise new technologies and give recommendations on whether, they should be funded and be available in the National Health Service (NHS). To work out the cost effectiveness, metrics are required. For evaluation of cost effectiveness, it is not just the price of the intervention but also the price of ongoing monitoring and of any adverse effects that may occur (Vergel et al, 2008). Some evaluation metrics also include any workdays lost by the patient to calculate the impact on society. Most new technologies, as a rule, in general are costly. However, on rare occasions they can be less costly than the comparator. Vergel et al state that in such instances, there is generation of ‘opportunity costs. NICE uses Quality Adjusted Life Years (QALY) to capture health related quality of life (morbidity) as well as increase in life span.
(mortality) together and homogenise the outcomes into a single metric. Although used by NICE as a formal methodology for economic evaluation, there is criticism of QALYs on the basis of equity as it does not take into consideration age, ethnicity and health status (Vergel et al, 2008). Other concerns around QALYs are that it is problematic to collect Health Related Quality of Life (HRQoL) information from children, mentally diverse and severely ill people. NICE uses QALY measures which are based on EQ5-D scheme using five dimensions of health on the level of severity i.e. ‘mobility’, ‘self-care’, ‘usual activities’, ‘pain/discomfort’, ‘anxiety/depression’ and NICE justification of the evaluation metric methodology is that it is based on UK population.

The opponents of current QALYs such as Paul Dolan and Daniel Kahneman, favour that ‘experiences’ of people should be factored in as a comparator when measuring HRQoL. Others following Amartya Sen’s school of thought propose a health capability model of economic evaluation (Wolf, et al, 2012). There is also difference of opinion on who the evaluators of the health state should be. Wolff et al, suggest three options for consideration: 1) the general public, 2) patients, 3) expert professionals. There are various approaches of measuring health outcomes so in terms of implications to health policy, it is an imperative to analyse and critique these methodologies. However, as case scenarios Wolff et al deliberate on the above three approaches and profess that if the final output is very similar to the current methodologies such as QALYs used by NICE, it may be best to remain with existing health evaluation methodology. Nonetheless, on further analysis of the different perspectives, Wolf et al conclude that the comparators may fall into the dimensions of EQ-5D but where the values may differ, it is justifiable to use the deliberative methodology to arrive to a final consensus. Similar to the WHO Disability Adjusted Life Years (DALY) methodology.

DALY, like QALY have been designed by the WHO to measure morbidity and mortality. Arnesen and Nord (1999) state that there is criticism of DALY in the way it oversimplifies complex information into a
single metric. Some of the criticism is around the lower societal value attached to disability and the weighting disadvantages children, women and older people. The cost effectiveness analyses seem to suggest the healthier a person, the more value is attached to them. The value of a person in accordance to how they function is in direct contradiction to how it is stated in the Declaration of Human Rights, “recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation.” and WHO aims to promote efficiency, equity and equality which does not seem to be the case with DALY. Arnesen and Nord (1999) conclude that these anomalies need to be addressed in the revised DALY protocol.

Orr and Wolf (2015) argue that with the cost of expensive treatments to prolong an individual’s life, brings into conflict of whether to save an individuals’ life against the human right to life against expenditure of funds towards the total good. This everyday decision of cost-effectiveness brings about the dilemma of an individuals’ right to life versus overall societal health benefit.

In the new era of global health research, there are more and more collaborations and partnerships. At times, different actors have their own agendas. Pharmaceutical industries, governments, academics and others collaborate in research studies to develop new scientific knowledge and evidence base. More and more research is taking place in LMIC where there is a higher burden of disease and it is cheaper to conduct research but this is not without ethical challenges. The power imbalance between HIC, who invariably are funding the research and LMIC has ethical implications of inequity and injustice. Some scholars claim imperialistic connotations with respect to ownership of intellectual property etc. The lack of adequate research infrastructure in underdeveloped countries can also be problematic and throw ethical complexities. However, in the pursuit of knowledge, capacity building in LMIC and bi lateral and multi-lateral learning particularly in emergency situations and pandemics, it is vital to continue to collaborate. On a positive note, there are also more and more examples of good practice
in research with co-creation with communities, capacity building, sustainability and LMIC researchers leading research.

The International Ethical Guidelines for Health-Related Research Involving Humans, specifically Guideline 8 on Collaborative partnerships, Capacity-building for Research and Research Review, states: “The desired relationship is one of equal partners whose common aim is to develop a long-term collaboration through South–South and North–South cooperation that sustains site research capacity. To safeguard against power differences, innovative forms of collaboration should be considered” Scholars debate on the pros and cons of research partnerships. Those favouring claim the benefits of exchange of knowledge, ability to access new technologies, professional mentorship, scientific expertise and low cost of instruments (Parker and Kingori, 2016). On the contrary, others suggest the word ‘collaboration’ to have colonial undertones and smacks of ‘intellectual colonialism’ stealing ideas from under developed countries, resulting in unequal North-South power around co-ownership, intellectual property rights etc (Guzman et al, 2017). The normative reaction to emergencies is of humanitarian efforts taking centre stage. However, undoubtedly research is the only way to gather new knowledge about the disease and mode of treatment. Consequently, global collaborations and partnerships particularly in times of emergency such as pandemics is an ethical exigent.

3.4.8 Towards a universal health coverage and progressive realisation of rights

With increasing interest in global health and the UN’s mandate of health for all, UHC, there is more and more research happening in the global south and in LMIC. This gives rise to further ethical and human rights considerations where the populations are less aware or are able to stand up for their human rights (Mills and Singh, 2007). This necessitates that vulnerable participants’ interests and human rights
are protected. Mills and Singh cite an example of a US funded study with Thailand partnership, on HIV in Thailand in early 2000, where US funds were not allowed to be used to supply clean needles to participants. Although, according to Article 29 of the Declaration of Helsinki, “benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic” interventions. The question that arises here is; should domestic law contravene a human rights agreement signed by both countries medical associations? This and other case studies on global health research illustrate that although there are many international instruments for conducting good research practice such as the Declaration of Helsinki, The Nuremberg Code and the ICH Good Clinical Practice (GCP) as discussed above, global health research brings in added complexities rather than just ethical and legal human rights law frameworks. Since the above instruments are not legally binding, it is problematic to enforce them. As the cost of research increases, more and more research is being conducted in LMIC. Mill and Singh recommend a list of considerations for researchers undertaking research in countries with diverse setting including research to be health promoting and to improve and sustain local health conditions rather than to benefit science and to increase scientific knowledge. Additionally, local consultation and local decision making would be an important first step towards culturally valid research.

The advancement of new treatments and medical discovery is dependent on research therefore research plays a fundamental role in innovations by pharmaceutical industries. As already stated, increasingly trials are conducted in diverse and unequal contextual settings which arguably poses an innate risk to the human participants of research subjects (Craddock, 2017). The externalisation of research by pharmaceutical companies to places like South Africa, Eastern Europe, Asia, and Africa where there is high prevalence of disease and the poor peoples’ access to drugs and healthcare is problematic.
Participation into a clinical trial maybe the only route to accessing treatment (Petryna 2009; Sunder Rajan 2006; Fisher 2008; Glickman et al. 2009). The ethical issue here is that generally these poor populations are not the end consumers of these treatments and do not benefit by the results of the trials (Petryna 2009) as has recently been in the case of Covid 19 vaccination stock being first bought out by the affluent western nations. Only what was left over ended up in these LMICs.

Another issue that Craddock raises is that the controlled environment of clinical trials do not emulate the complex condition of the settings that the trial is being conducted in as the researchers do not want to contaminate the data by introducing other interventions. The notion of ‘informed’ and ‘consent’ due to literacy, language and other cultural confounders pose further ethical dilemmas. The rigidity of the international funders of clinical guidelines on adherence to the western models of guidelines pulls researchers towards generating scientific evidence base above the participants’ welfare (Craddock, 2017). In order to equalise some of this imbalance between funders and host countries, building research capacity and capability and developing research networks is urgently required (www.who.org). Craddock concludes that instead of debating the ethical question of ‘doing no harm’ to the human subjects, scientists are approaching the inequality question by taking a wider approach such as sharing of benefits, community engagement and empowerment by developing scientific knowledge, training and practices locally. In this way, deploying the social value of research. Additionally, Craddock states that the scientific debate on data integrity etc continues so that the clinical trials abide by the regulatory requirements but is it better to reduce the distance between ‘laboratory conditions’ and ‘real world circumstance’?

According to Trouiller et al, 2002, considerable progress has happened in the development of knowledge base and development in communicable, infectious diseases which are mainly burden of disease of under-developed countries. As much as the need for affordable,
effective, and efficacious treatments is required, pharmaceutical industries have virtually stopped development due to low return on investment (Pecoul et al, 1999). Trouiller et al 2002 state that the rationale from pharmaceutical industry is that research and development is ‘risky and costly’ and therefore, divert investment towards HIC which have run schemes such as health insurance in Europe and the NHS in the UK. The importance of collaboration between HIC and LMIC is well acknowledged for sometimes now but the perspectives of equity and justice persist in order to reduce the hierarchical make up of this relationship. (Pratt and Hyder 2016). An attempt to plug the gap in research and development is public/private partnerships where pharmaceutical industry works with Not for Profit organisations and academia. These ventures have produced results in treatment development.

Dal-Re et al, 2016 argue that inequity of access to healthcare is acknowledged and evidenced widely in literature. However, it is important to recognise the health inequity within HICs such as North America and Europe, in particular Southern Europe where immigrant and refugee populations may have access to community care through NGOs but unable to access full healthcare due to their non-eligibility status. Consequently, they carry a higher burden of disease and become more likely subjects for recruitment into clinical trials. Dal-Re et al allege it is high time that these inequalities are addressed and they suggest, a holistic approach with targeted benefits from the trial sponsors towards the trial participants’ needs.

3.4.9 Community priorities and participation

In recent years, Public and Patient Involvement and Engagement (PPIE) has become an important and necessary element within research and there are more and more public and private collaborative trials using frameworks to engage patients and to get patient perspectives within the trial design, implementation, and patient involvement throughout the trial cycle (Lavitan et al, 2018). Apart from
having ethical and moral grounds for applying evidence-based medicine to individual patients, health needs assessments and commissioning innovative technologies, Patient and Public Involvement (PPI) or community engagement in design of technologies and methods promotes Community ‘acceptance’ (Staley et al, 2006). The practical benefits of PPIE are the lived experience and insight into the disease which adds rigour to the research question, helps with recruitment and retention and improves buy in and experience of the patient (Smith et al, 2016). However, Mader, et al, 2018 report that there remains incongruity between what the patients consider as a priority (quality of life) to the funders of research (cost effectiveness and efficiency). As already stated, PPIE although an integral component of research design, it remains limited and tokenistic (Mader, et al 2018). PPIE in UK is relatively new, in 1991 the NHS developed the first NHS Research and Development Strategy (Peckham, 1991). In 2015, following a research study led by Polycystic Kidney Disease (PKD) charity in collaboration with Cambridge Clinical Trials Unit (CCTU), a Patient Led Research Hub was launched with the aim to input scientific and research support to initiatives led by patients.

3.4.10 Y-CMAP Patient and Public Involvement and Engagement

The YCMAP research team involved local patient and/or community groups in developing the trial design. The team also have service users on the oversight committees and benefitted greatly from the involvement of service users and the public. The comments and feedback were incorporated in the proposal. One of the main outcomes in the YCMAP exploratory trial (Husain N et al, 2014) and the CMAP full trial was increasing awareness about mental health problems in the community. Stakeholder events were held during the exploratory trial and continued as part of the ongoing trial which offered Patient and Public Involvement (PPI) opportunities. The research team ensured extensive patient and public involvement, including their input in
adaptation of the psychological intervention. Community workshops for further PPI engagement and to share findings with the community were held. Feedback from these talks were taken and interviews were conducted to gain further qualitative information. During the discussions with the service user collaborators, the research team sought to understand their experiences, what support they received, what support could be adapted to be more appropriate for this specific population. The team worked with the PPI members to finalise the research study methods and aims and the format of the therapy etc so that it will be most useful for adolescent self-harm patients. Ongoing involvement with patient and community group is planned throughout the proposed research project as it has greatly helped the team, not only in recruitment and retention of participants in the ongoing trial and previous studies but also in dissemination of the findings to key community influencers. There are plans to work with the advisory group who are instrumental in engaging with the community. Service users on the advisory board will be trained in research methods. The research team has significant expertise in this area and has trained over 70 users & carers in research methods. An annual course on qualitative research methods is organised and the service users are always invited to attend. Three service users have joined as collaborators on the project. The service users’ advisory group will be involved in the development of the Participant Information leaflets and the interview guides for the one-to-one interviews. Working closely with the research team they will contribute to the interpretation of the qualitative data. They will also work with the team in the writing of lay summary of the research. The team continues to work with the media partners to raise awareness and help reduce stigma of mental health issues.

3.4.11 Conclusion

As more and more interest is developing in global health research, there is more research in LMIC due to burden of disease, larger population sizes and lower cost of conducting research, it becomes an
ethical imperative of the global scientific community to ensure that research is methodologically relevant and culturally sensitive to the diverse settings, that research delivers social value and upholds the rights of the human subjects. Despite there being similar CBT based research in western countries, cultural adaptation of YCMAP essentially contextualises the intervention although some of the components of CMAP may have benefitted adolescents, the key differences in the characteristics of children and adults deem CMAP not to be externally valid in young people. Additionally, the literature review show that no studies for effectiveness of any culturally appropriate interventions have been done to address the unmet need for prevention of self-harm and suicide in the young population in LMIC. YCMAP unlike the South African case law will be crucial step towards realising progress on accessibility of culturally sensitive treatment for self-harm in Pakistani adolescents where none exists.

Positionality and Methodologies

I, the researcher am a female aged 69 yrs who is of Pakistani heritage. My father was a psychiatrist in the Pakistan Armed Forces. Having been born and brought up in a protected environment of an air force base, I married at the age of 18 years and came to the UK. I speak both English and Urdu fluently. My undergraduate and post graduate education was completed in the UK at the same time as raising my two boys and pursuing my career in the NHS. As alluded above, having led a sheltered upbringing in the air force base which had its own school, cinema and other amenities meant that I remained in an environment which is synonymous of most armed forces bases globally. This meant I had limited exposure to ‘real life’ Pakistan and am not sure how much of a cultural insider I am from the perspective of knowing the real issues of Pakistan. However, all through life, I have remained connected to my Pakistani roots and have tried to give back to the country that brought me up, through charitable pursuits and by way of
developing capacity and capability in Pakistan. My PhD provided this unique opportunity to examine the cultural values as an insider/outsider. This had its strengths as the clinicians were very open and honest during their interviews as they felt comfortable with sharing ‘warts and all’ with ‘one of their own’. The limitation could be that I may have brought in my own biases by making the assumption that I know my culture well. However, we know that there are many subcultures in Pakistan as revealed in our focus group discussions. Also, having a background in health services, my research provided me with an opportunity to work with clinicians and researchers in Pakistan to investigate the health system and the ethical dilemmas faced in conducting research in the landscape where the clinicians are trained in the western biomedical model but are faced with the environmental, cultural, religious, and social complexities of a very different context. More importantly, I wanted to investigate whether the clinicians’ own preferences based on their own belief systems had an impact on their decisions, when recruiting patients into RCTs and whether those involved in conducting trials’ preferences were different from those not involved in research.

I, the researcher used an exploratory mixed methods approach to investigate how cultural, moral, and religious values relate to western concepts of research ethics.

These methods that I have used include both, qualitative and quantitative approaches. Mixing the two approaches has allowed me to collect and analyse data within the same research study (Bowers et al, 2013, Creswell JW et al, 2011) The methodological triangulation of data provides rigour in terms of the use of interdisciplinary methods (Denzin, 1970; 1978). It has helped to draw the potential strengths of both quantitative and qualitative methods (Shorten A et al, 2014) and allowed exploration of diverse perspectives and helped unravel intricacies and relationships between the multi layered research questions. Inductive analysis of the normative questions around the
moral justification of multi centred randomised clinical trials such as YCMAP as well as an empirical study of the views and values of practitioners and members of policy bodies. The latter includes members of the ministry of health and clinicians. The rationale to gathering policy makers’ views was to gauge how much evidence they would require to persuade them to adopt the psychological interventions as standard care. I used the following methods to gather data:

- Survey of clinicians, those recruiting patients to YCMAP and those not involved in the trial
- Cultural inquiry through focus group with indigenous researchers.
- Interviews with clinicians, those recruiting patients to YCMAP and those not involved in the trial
- Interviews with government policy makers in Pakistan

Chapter 4 Quantitative Research Methodology

4.1 Survey Study design

I conducted a cross-sectional survey of clinicians involved in the YCMAP at all five sites (Karachi, Lahore, Rawalpindi, Hyderabad and Peshawar Pakistan) of the trial (N = 35) and of clinicians not involved in the trial (N = 40) but practising in the same geographical areas.

The survey included clinicians using convenient sampling from a mix of private and public healthcare settings including Karachi, Lahore, Rawalpindi, Hyderabad, and Peshawar Pakistan. The data was collected from May 2019 to December 2019. The YCMAP research team first took ‘consent to contact’ from the clinicians and then the visiting research assistants personally scheduled the meeting with clinicians to complete the survey questionnaires.
The survey was to answer the following research question:

Whilst awaiting the findings of the YCMAP trial, how relatively effective do clinicians participating in recruitment for the trial think that Talking Therapies are in young people, how does this compare to the views of clinicians not participating in recruitment for the trial and whether there was uncertainty in clinicians to justify conducting a Randomised Clinical Trial?

The objectives of the survey were:

- To assess which intervention is preferable? YCMAP plus TAU compared to TAU only for young patients at risk of self-harm and suicide as measured by the responses of clinicians both involved in the trial and those not involved in the trial
- To determine whether there is uncertainty in clinicians to justify conducting Randomised Clinical Trial

A total of n=35 clinicians involved in the trial and n=40 clinicians not involved in the trial were surveyed.

4.1. Questionnaire Design

I adapted the questionnaire from a previously validated survey questionnaire originally intended to assess therapeutic misconception in patients when they consent to research. The self-administered questionnaire, based on the Therapeutic Misconception (TM) Scale (Appelbaum, 2012), was designed to find out whether or not clinicians have personal preferences for either of the two treatments currently offered in the RCT (YCMAP). The adaptation process was a step wise approach. I had an initial discussion with my supervisor to decide what data was required and selected areas to include. I then designed the questions, carefully choosing the wording to ensure the questions were clear and understandable. I then discussed the layout and presentation with my supervisor. The 1st draft was then sent to my 2nd supervisor for comments and feedback.
In January 2019, the prototype questionnaire was piloted with the help of four clinicians: two psychiatrists and two GPs, to test the contextual fitness (Horner et al, 2014) and face validity of the questionnaire. Background information was provided in the form of previous relevant trial results on the effectiveness of interventions for adults who self-harm (Husain et al, 2014). Following advice from the PILL Advisory Group and in discussion with supervisors, response options were amended to avoid a central tendency in responses (reducing from five options to four) (Simms et al., 2019) (see appendix 1).

Data on the views of recruiting clinicians was collected using 4-point Likert scale. Participants in this trial are young people aged 12 to 18. On entering the trial, they are randomised to receive either YCMAP plus TAU or TAU alone. YCMAP is a new treatment that has been culturally adapted by Pakistan Institute of Living and Learning (PILL). I was interested in finding out what level of evidence clinicians would want before prescribing this new psychological treatment routinely.

4.1.2 Ethics Approval

Ethical approval for the survey of clinicians was required both in the UK and in Pakistan. The survey was deemed to be minimum risk by Science and Technology Studies (STS), UCL guidance. STS departmental ethics approval was granted in May 2019 (Ref. STSEth159).

In Pakistan, both the qualitative and quantitative methodology of this study formed part of the overall trial ethics approval. The Pakistan National Bioethics Committee granted approval in November 2019 (Ref. NBC-419).

4.1.3 Participants and recruitment

Initially, it was planned to send the survey materials to the clinicians by my UCL email address. However, PILL senior researchers advised
against this method. PILL has been conducting mental health research in Pakistan since 1998. Their experience over the past 23 years suggest, that busy clinicians do not engage via email and therefore the response rate to email surveys in Pakistan is very poor. Also, as per PILL confidentiality policy, PILL contacted potential recruits to protect their confidentiality from myself (the researcher). The advice from PILL was for the YCMAP team to first elicit ‘consent to contact’ from the clinicians and then the visiting research assistants to personally take the survey questionnaires to the clinicians at the five YCMAP sites in Pakistan. To recruit clinicians not involved in the Y-CMAP trial, we conducted convenience sampling from a mix of private and public healthcare settings including Karachi, Lahore, Rawalpindi, Hyderabad and Peshawar Pakistan. These were mostly settings where PILL centres are based and had working relations with.

The data were collected from May 2019 to December 2019; a period during which trial recruitment was ongoing and before the RCT results were known. Based on PILL senior researchers’ advice, the final process followed was as in figure 3
The same process was followed to survey clinicians not involved in the YCMAP trial. These were clinicians working on other projects with PILL.
4.2 Survey Statistical Analysis

I estimated that a minimum sample size of 50 cases was needed to detect significant group differences in proportions agreeing with statements (Namuth-Covert et al., 2012). I compared the socio-demographic characteristics of those involved in recruiting to the trial, and those not involved in the trial, using Chi² tests. My statistical hypotheses were:

1. There is likely to be significant differences in clinicians involved in recruiting to the trial as compared to clinicians not involved in recruiting to the trial regarding treatment preferences (YCMAP plus TAU or TAU only) for young patients at risk of self-harm.

2. There is likely to be a collective uncertainty in clinicians (i.e. equipoise) to justify conducting a RCT despite personal preferences.

I used Pearson Chi² test to investigate group differences in the proportion of those expressing different views relating to equipoise in a trial of an intervention for young people at risk of self-harm. Fisher exact test was used to determine normality of data. SPSS version 23 was used for statistical analysis of data. Preliminary analyses were performed to check the assumptions of normality and linearity.

4.3 Key findings of the survey

4.3.1 Descriptive statistics

Response
Initially, 78 clinicians were approached of whom 75 completed the survey questionnaire. A total of 75 clinicians participated in the survey. We recruited n=35 clinicians involved in recruiting patients to the trial (46.7%), and n=40 not involved in the trial (53.3%), representing a response of 92% for the former group and of 100% for the latter group, and an overall response of 96%.

Demographic data
Descriptive statistics of the study data showed no significant demographic differences between the two groups i.e., p > .05. The
mean age of clinicians involved in the trial was M= 30.65 and the mean age of those not involved in the trial was M= 31.07 (p > .847). The mean number of years since graduation of involved in the trial was M= 5.80 (SD= 8.6) and hose not involved in the trial was M= 6.92 (SD= 9.1) with minimum 1 year since graduation to maximum 35 years of graduation. There were no significant differences in medical speciality between two groups (p= > .05). Among the group involved in the trial vs not involved in the trial, around 22.9% vs 15.0% were general practitioners, 22.9% vs 12.5% were psychiatrists, 2.9% vs 5.0% were ED doctors, 17.1% vs 27.5% were medical ward doctors, 5.7% vs 17.5% were surgical ward doctors and 28.6% vs 22.5% were from other medical specialties. Similarly, among those not involved in the trial, around 42.9% were general practitioners, 38.5% were psychiatrists, 66.7% were ED doctors, 35.3% were medical ward doctors, 22.2% were surgical ward doctors and 52.6% were from other medical specialties (see Table 9). Descriptive statistics of the study data showed no significant demographic differences between the two groups i.e., p > .05. The mean age of clinicians involved in the trial was M= 30.65 and the mean age of those not involved in the trial was M= 31.07 (p > .847). The mean number of years since graduation of involved in the trial was M= 5.80 (SD= 8.6) and hose not involved in the trial was M= 6.92 (SD= 9.1) with minimum 1 year since graduation to maximum 35 years of graduation. There were no significant differences in medical speciality between two groups (p= > .05). Among the group involved in the trial vs not involved in the trial, around 22.9% vs 15.0% were general practitioners, 22.9% vs 12.5% were psychiatrists, 2.9% vs 5.0% were ED doctors, 17.1% vs 27.5% were medical ward doctors, 5.7% vs 17.5% were surgical ward doctors and 28.6% vs 22.5% were from other medical specialties. Similarly, among those not involved in the trial, around 42.9% were general practitioners, 38.5% were psychiatrists, 66.7% were ED doctors, 35.3% were medical ward doctors, 22.2% were surgical ward doctors and 52.6% were from other medical specialties (see Table 9). A quarter (27.9%) of the sample reported having a relative or friend who had died by suicide, and 32.4%
reported having a relative or friend who had attempted suicide. There were no significant group differences, comparing those involved in recruiting to the trial and those not involved, on any of these characteristics.

**Missing data**

There were no missing data on any variable.

### 4.3.2 Statistical analyses between groups of clinicians

The study found that there were no significant group differences (p > 0.05) in the proportions agreeing with 9 out of 11 statements (see table 5 statement no. 1,2,5,6,7, 8, 9,10, and 11). The majority of clinicians involved in the trial (60%) and half of the health professions not involved in the trial (50%) disagreed with the statement that young people at risk of self-harm who are receiving Y-CMAP plus TAU in the trial may not do as well as they would on TAU alone (p> .05) (Table 5 statement no. 1). A high proportion of clinicians in both groups agreed that young people at risk of self-harm and suicide who are receiving YCMAP plus TAU may do better than TAU alone (Table 5 statement no. 2). Similarly, a significantly high percentage of clinicians involved in the trial (82.9%) and those not involved in the trial (65.0%) disagreed with the idea that YCMAP plus TAU may not be as effective as any TAU (p > .05) (Table 5 statement no. 5).

We found no significant group differences in the proportions reporting a preference for Y-CMAP plus TAU for young patients over TAU alone (over 85% in each group; p > .05; statement 6 in Table 5), or in the proportions agreeing that there is nothing on which to base a personal preference for Y-CMAP plus TAU over TAU alone for young patients (54.3% vs 75.0%, p > .05) (table 5 statement no. 7). Consistently, there were no significant differences found in reported personal preferences for YCMAP plus TAU despite collective uncertainty amongst the scientific profession (p = 0.367) and their reported confidence in this preference (statement no 8, and 8a in Table 5) (p = 0.564). Almost equal percentages in both group (more than 90%) agreed that they
were confident in their preference. More than 80% of clinicians in both groups agreed that possessing a personal preference for YCMAP plus TAU is morally permissible despite collective uncertainty amongst the scientific profession.

Nearly 91.4% of clinicians involved in the trial agreed that personal preference could be based on factors independent of a clinical judgement of relative efficacy (statement no. 9) compared with 85% of those not involved in the trial showing a non-significant difference (p > .05). Similarly, although there were no significant differences (p > .05), the majority of the clinicians involved in the trial (91.4%) and a nearly equal but slightly lower percentage of clinicians not involved in the trial (87.5%) agreed that randomised trial of Y-CMAP plus TAU and TAU alone is clinically needed despite any individual preferences for Y-CMAP plus TAU or for TAU alone (statement no. 10).

There were no significant differences found on the statement that the trial of Y-CMAP plus TAU and TAU alone should be sufficient to decide whether to offer YCMAP as a standard treatment for young people at risk of self-harm. Almost equal percentages of both groups (nearly 75%) agreed that the trial of Y-CMAP plus TAU and TAU alone should be sufficient to decide whether to offer YCMAP as a standard treatment for young people at risk of self-harm (statement no. 11).

Specific statements for which we found significant group differences were the following:

- We found that a significantly greater proportion of clinicians involved in the trial agreeing with the statement that treatment overall is better as a result of young patients’ participation in the Y-CMAP trial (90% vs 62.9%; p = 0.015; statement no. 3).
- Regarding the perceived availability of other treatment options for young people at risk of self-harm, a significantly greater proportion of clinicians not involved in the trial agreed with the statement that there are other treatments which might be just as good for young people (87.5% versus 48.6%; p < 0.05; statement 4 in table 5). However, a significant majority of
clinicians involved in the trial (51.4%) as compared to those not involved in the trial (12.5%) disagreed with this statement (p < 0.05) (Table 5 statement no. 4).

It is remarkable to discover a large number of health professionals who have known someone in family or friends who had attempted suicide or have died by suicide 19 (27.9%) of health professionals have known someone amongst their friends or family who died by suicide and 22 (32.4%) of them also had known someone in their family or friends who attempted suicide). It is to be noted that although health professionals were asked only to respond to these two questions if they felt comfortable about it. All health professionals opted to respond. As equal numbers of clinicians reported this personal experience. Therefore, it does not appear to have any bearing on their preference of treatment.
Table 4. Sociodemographic characteristics of participating clinicians (N= 75)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Those involved in the trial (n=35)</th>
<th>Those not involved in the trial (n=40)</th>
<th>Total (N=75)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>30.65 (8.9)</td>
<td>31.07 (9.7)</td>
<td>30.8 (9.28)</td>
<td>.847</td>
</tr>
<tr>
<td>Years since graduation from medical school</td>
<td>5.80 (8.6)</td>
<td>6.92 (9.1)</td>
<td>6.4 (8.89)</td>
<td>.588</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 17 (40.5)</td>
<td>25 (59.5)</td>
<td>42 (56.0)</td>
<td>.225</td>
</tr>
<tr>
<td></td>
<td>Female 18 (54.5)</td>
<td>15 (45.5)</td>
<td>33 (44.0)</td>
<td></td>
</tr>
<tr>
<td>Medical specialty</td>
<td>GP 8 (57.1)</td>
<td>6 (42.9)</td>
<td>14 (18.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychiatrist 8 (61.5)</td>
<td>5 (38.5)</td>
<td>13 (17.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ED Doctor 1 (33.3)</td>
<td>2 (66.7)</td>
<td>3 (4)</td>
<td>.380</td>
</tr>
<tr>
<td></td>
<td>Medical ward doctor 6 (35.3)</td>
<td>11 (64.7)</td>
<td>17 (22.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical ward doctor 2 (22.2)</td>
<td>7 (77.8)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other medical specialty 10 (52.6)</td>
<td>9 (47.4)</td>
<td>19 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Do you know anyone amongst your friends or family who has died by suicide?</td>
<td>Yes 10 (14.7)</td>
<td>9 (13.2)</td>
<td>19 (27.9)</td>
<td>.787</td>
</tr>
<tr>
<td></td>
<td>No 24 (35.3)</td>
<td>25 (36.8)</td>
<td>49 (72.1)</td>
<td></td>
</tr>
<tr>
<td>Do you know anyone amongst your friends or family who has attempted suicide?</td>
<td>Yes 11 (16.2)</td>
<td>11 (16.2)</td>
<td>22 (32.4)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>No 23 (33.8)</td>
<td>23 (33.8)</td>
<td>46 (67.6)</td>
<td></td>
</tr>
</tbody>
</table>

n = number, % = percentage, p-value = level of significance, GP = General Practitioner, ED = Emergency Department. For continuous variables (i.e., age and years since graduation from medical school), mean and standard deviations are reported.
Table 5. Proportions of survey participants agreeing with each statement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Those involved in the trial (n=35)</th>
<th>Those not involved in the trial (n=40)</th>
<th>Total (N=75)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Young patients at risk of self-harm who are receiving Y-CMAP plus TAU in the trial may not do as well as they would on TAU alone.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>14 (40.0)</td>
<td>20 (50.0)</td>
<td>34 (45.3)</td>
<td>.263</td>
</tr>
<tr>
<td>Disagree</td>
<td>21 (60.0)</td>
<td>20 (50.0)</td>
<td>41 (54.7)</td>
<td></td>
</tr>
<tr>
<td>2. Young patients receiving Y-CMAP plus TAU may do better than they would on TAU alone.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>34 (97.1)</td>
<td>37 (92.5)</td>
<td>71 (94.7)</td>
<td>.360</td>
</tr>
<tr>
<td>Disagree</td>
<td>1 (2.9)</td>
<td>3 (7.5)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>3. Treatment overall is better as a result of young patients’ participation in the Y-CMAP trial.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>22 (62.9)</td>
<td>36 (90.0)</td>
<td>58 (77.3)</td>
<td>.015</td>
</tr>
<tr>
<td>Disagree</td>
<td>13 (37.1)</td>
<td>4 (10.0)</td>
<td>12 (22.7)</td>
<td></td>
</tr>
<tr>
<td>4. There are other treatments outside this study which might be just as good for them.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>17 (48.6)</td>
<td>35 (87.5)</td>
<td>52 (69.3)</td>
<td>.000</td>
</tr>
<tr>
<td>Disagree</td>
<td>18 (51.4)</td>
<td>5 (12.5)</td>
<td>23 (30.7)</td>
<td></td>
</tr>
</tbody>
</table>
5. Y-CMAP plus TAU may not be any more effective than any TAU.
<table>
<thead>
<tr>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (17.1)</td>
<td>29 (82.9)</td>
</tr>
<tr>
<td>14 (35.0)</td>
<td>26 (65.0)</td>
</tr>
<tr>
<td>20 (26.7)</td>
<td>55 (73.3)</td>
</tr>
<tr>
<td>.068</td>
<td></td>
</tr>
</tbody>
</table>

6. I think that the Y-CMAP plus TAU is preferable to TAU alone for young patients.
<table>
<thead>
<tr>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 (88.6)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>36 (90.0)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>67 (89.3)</td>
<td>8 (10.7)</td>
</tr>
<tr>
<td>.566</td>
<td></td>
</tr>
</tbody>
</table>

7. There is nothing on which to base a personal preference for Y-CMAP plus TAU ahead of TAU alone for young patients.
<table>
<thead>
<tr>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (54.3)</td>
<td>16 (45.7)</td>
</tr>
<tr>
<td>30 (75.0)</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>49 (65.3)</td>
<td>26 (34.7)</td>
</tr>
<tr>
<td>.051</td>
<td></td>
</tr>
</tbody>
</table>

8. Personal preference for YCMAP plus TAU is permissible despite collective uncertainty amongst the scientific profession.
<table>
<thead>
<tr>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (85.7)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>32 (80.0)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>62 (82.7)</td>
<td>13 (17.3)</td>
</tr>
<tr>
<td>.367</td>
<td></td>
</tr>
</tbody>
</table>

8a. I am confident in this preference.
<table>
<thead>
<tr>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (94.3)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>37 (92.5)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>70 (93.3)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>.564</td>
<td></td>
</tr>
</tbody>
</table>
9. A personal preference could be based on factors independent of a clinical judgement of relative efficacy.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
<td>32 (91.4)</td>
<td>34 (85.0)</td>
<td>66 (88.0)</td>
<td>.312</td>
<td></td>
</tr>
<tr>
<td>Disagree</td>
<td>3 (8.6)</td>
<td>6 (15.0)</td>
<td>9 (12.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. The randomised trial of Y-CMAP plus TAU and TAU alone is clinically needed despite any individual preferences for Y-CMAP plus TAU or for TAU alone.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
<td>32 (91.4)</td>
<td>35 (87.5)</td>
<td>67 (89.3)</td>
<td>.434</td>
<td></td>
</tr>
<tr>
<td>Disagree</td>
<td>3 (8.6)</td>
<td>5 (12.5)</td>
<td>8 (10.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. The trial of Y-CMAP plus TAU and TAU alone should be sufficient to decide whether to offer YCMAP as a standard treatment for young people at risk of self-harm.

<table>
<thead>
<tr>
<th></th>
<th>Agree</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
<td>26 (74.3)</td>
<td>30 (75.0)</td>
<td>56 (74.7)</td>
<td>.576</td>
<td></td>
</tr>
<tr>
<td>Disagree</td>
<td>9 (25.7)</td>
<td>10 (25.0)</td>
<td>19 (25.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 5: Qualitative Research Methodology

5.1 Qualitative Study design
I collected qualitative data from three separate sources, all of which were key stakeholders of YCMAP: A range of qualitative data collection methods were employed to cultural context as well as an insight into the social and religious beliefs and norms of the researchers in a different research setting,

1) A focus group with 32 researchers. This was specifically to gain a deeper understanding, into the differences in religious and cultural beliefs and values as perceived by Pakistani researchers with a view to compiling a community engagement tool for western researchers.

2) A set of qualitative interviews with 20 clinicians to gain a fine-textured understanding of beliefs, attitudes, values, and motivations (Gaskell, 2000, p.39), of these individuals.

3) A set of conversations with 3 policymakers.

5.2 Cultural inquiry (focus group discussion)
Recognising values and engaging communities across cultures: Towards developing a cultural protocol for researchers (Memon et al, 2021)

The visit to Pakistan provided me, the researcher with an excellent opportunity to commence field work. A discussion group moderated by me with researchers, contributed towards gaining further insight into the cultural beliefs, norms and values. PILL is a non-profit organisation with a track record in mental health research. As in YCMAP, PILL has collaborated with western researchers on many projects. As part of community engagement, HIC researchers visit Pakistan and become involved in community engagement projects. Due to cultural differences and norms, they can sometimes come across as insensitive and can also be offended by the local indigenous communities. Misunderstandings can arise due to misinterpretation of body
language, gestures or insufficient knowledge of local beliefs and values.

As mentioned above, PILL has many visiting researchers from HIC, who are involved in community engagement, training and development. This provided an excellent opportunity for PILL and University College London (UCL), UK for collaboration to identify the gap and to gain an understanding of the beliefs, cultural norms, and values of local communities with the aim to; better understand and manage the differences in values and ethics in a different cultural setting. The rationale underpinning the development of a cultural protocol is that when there is no clear communication and understanding of the beliefs, culture, norms, nuances and values of a particular community, there is no foundation on which to build rapport, respect and trust needed for initiating the process of community engagement itself. If we believe in local participation and community engagement to be core values underpinning participatory approach, we need to make a concerted effort to gain insight into the belief system, norms and values of the communities we work with.

Researchers from five PILL sites (Karachi, Lahore, Rawalpindi, Quetta and Peshawar) took part. This insight into their lived experiences and narrative was invaluable.

**Setting:** The discussion group was convened on January 11th, 2019 at PILL head office in Karachi with four other PILL centres from different cities joining via zoom. The discussion was in English and Urdu to facilitate communication. The participants were researchers from PILL (n = 32), they were all qualified psychologists who had experience of community engagement and partnership relied research activities across Pakistan and had volunteered for the group discussion. The discussion group lasted for one hour and 28 minutes. Written consent was taken from all the participants to audio record the discussion and to use the materials for publication.
A semi structured list of questions to facilitate the discussion was developed following literature review. This explored researcher cultural beliefs and the impact on their research activities, their perception of challenges and responsibilities as a researcher coming from another country. The discussion was facilitated by myself (with a Masters in health services management and a background in implementation sciences). The group discussion revolved around the experiences and learning of local researchers from community engagement activities.

**Table 6: Participants Demography**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Participants n=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 31.46 years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Baluchi</td>
<td>4</td>
</tr>
<tr>
<td>Pathan</td>
<td>4</td>
</tr>
<tr>
<td>Punjabi</td>
<td>10</td>
</tr>
<tr>
<td>Sindhi</td>
<td>8</td>
</tr>
<tr>
<td>Urdu speaking</td>
<td>6</td>
</tr>
</tbody>
</table>

**Analysis**

The audio recording of discussion was transcribed by myself. The transcription was translated into English by a bilingual researcher (MA). Translated transcript was then back translated into Urdu for checking by an independent researcher. I used the approach of thematic analysis to analyse the discussion (Braun and Clarke 2006). Steps involved in the analysis included familiarisation, generating initial codes, searching for themes, reviewing themes, defining, and naming themes and finally transforming it in a report form. I did initial line by line coding and finalising the themes. I was supervised by an
experienced qualitative researcher (TK) to maintain data credibility and trustworthiness. TK reviewed the transcript and analysis.

Focus Group findings.

The aim of this initiative is to present findings from a discussion group towards development of a cultural protocol for researchers for community engagement in Pakistan. A culture protocol for researchers is not intended as a substitute for community engagement which itself is an important process for eliciting views and values of particular communities and relates to particular research proposals and projects. A cultural protocol, however, would prepare researchers to approach the process of community engagement with respectful cultural sensitivity.

The results presented here are based on the general themes that emerged from the discussion. The five themes from the discussion include: i) religious principles and rules, ii) concept of autonomy and privacy, iii) notion of respect and trust, iv) cultural differences (etiquette) and v) custom and tradition (gift giving and hospitality). The five themes which emerged from the discussion are as follows and the key messages from these five themes are in Table 7:

i) Religious principles and rules

Following British colonial rule in India, Pakistan was founded in 1947 on the basis of religion; Islam. Hence, religion and culture are very much intertwined. Most societal norms are underpinned by religious beliefs. The community religious leaders once engaged can be great allies. This was stated in the Group “I think it is better to get hold of the imam in the community first. He prepares the ground for us by telling them who we are? And what we are trying to do? It makes our work much easier”.

As Islamic traditions and practices are virtually ingrained in all parts of Pakistani life, it is an imperative to understand the significance that prayer, religious festivals and festivities have in everyday life. This was
expressed several times in the discussion Group “If it is prayer (namaaz\(^2\)) time specially Friday (Jummah) prayer we should not work during that time. Also, late afternoon (Asar prayer) and at sunset (Maghrib prayer). These prayer times are important so there should not be a clash with these times”. Prohibition of food in Ramadan and music and other festivities during the month of Moharram were also mentioned “During Ramadan people will be offended if you eat in public as everyone should be observing fast” “In Moharram, especially in Shia Sect we don’t play music or watch movies as it is the month of mourning”.

Islamic ideals and customs were further reiterated. A discussant mentioned “We do Qurbani (slaughter of an animal in the name of Allah) on Eid ul Adha. It may be shocking for foreigners but it is our religion, we do it in the name of Allah”

ii) Concept of Autonomy and privacy

It would be quite usual for the whole family to be involved in discussions and decision making on issues which in the HIC maybe perceived as violation of autonomy. The tension between the primacy of autonomy in HIC bioethics literature is sometimes in contrast and incompatible with the social value system of interconnectedness and interdependence within cultures such as Pakistan which are religiously grounded. “The whole families come and attend clinic with the patient. When people travel from far away villages, they have to camp outside hospitals for days as it is too costly and too far to go home every day”

Respect for the elders of the family and especially the husband in a male dominated society make ‘surrogate’ decision making an expectation and the norm. “….. People come with their mother, husband, sometimes also friends. Mostly husband or mother will speak for them and decide.”

\(^2\)Islamic worship
iii) Notion of Respect and Trust

Distrust still exists within the (illegal) migrant community fleeing from Afghanistan to Pakistan since the Afghanistan war, as they may not possess identity cards. Young men dressed in foreign clothes are perceived to be government officials. “So again it is related to credibility, integrity and trustworthiness. We experience in Orangi Town (in Karachi) that they don’t trust us. Actually as we are young men dressed in foreign clothes so they think that we are someone else, I mean they think we are ISI (Intelligence Services) or like that”

As segregation still exists in most families, traditionally male researchers will be restricted from home visiting. This was expressed by a discussant “Only females can visit homes, male have to wait outside”.

However, being respectful to customs and traditions goes a long way to build trust. As someone in the Group said “if you sit on the chair and others are sitting on the floor, it is not good. It is all about respect”. Family and family loyalties are held sacred in the Pakistani culture and social fabric of the society. This value system is derived from the Islamic belief of individual and collective responsibility for the welfare of kin and kinship. This translates into family loyalty as long as the family member fulfils the criteria. Be it nuclear or extended, family comes above other social relationships and even commercial arrangements. As one discussant in the group alluded “My uncle who is a cloth merchant wanted me to manage his shop when I completed my university education”.

iv) Cultural Differences (Etiquette)

Eye contact and physical touching between genders is considered disrespectful and an invasion of privacy. Eye contact with the elders is considered to be challenging to the status of the elders and therefore also disrespectful and rebellious. The cultural polarisation of understanding of the same gestures between cultures can be
perceived as disrespect, misunderstanding and offensive; this can be detrimental to community engagement and distrust of researchers from HIC. “Making eye contact with your elders and opposite gender is considered disrespectful”.

The segregation of genders historically, religiously and traditionally has required ‘Pardah’ separation between male and female outside the family confines. This cultural conditioning and tradition continues. As observed by one discussant: “Foreign professionals need to consider the cultural values before visiting other cultures. As most people don’t like to sit close to them or do hugs. Female professionals hesitate in sitting close with male foreigners”. The point was further reinforced by another “The girls don’t even shake hands with the boys, when they greet each other, girls’ shake hands with each other but not with the boys”.

A similar comment was made in the Group: “You should prefer to wear long shirts with shawl and avoid wearing shorts or wear shawl or scarf”. Is this relevant to female or is it relevant to male? “Yes, both - So, they just should not go in shorts and t-shirts. Not shorts just jeans, trousers and shirts are best for male”.

The dress code signifies not only adherence to cultural norms of modesty but also signals religious significance. “I believe if people coming in foreign dress, they are seen as having more professional attitude, and coming with more professional background. They are having some kind of knowledge and people take them very seriously. Their comments and suggestions on any issue are taken very seriously”.

Interestingly, personal space and boundaries are not the same as in the west. People may stand quite close when communicating. Also, albeit out of respect they may call male ‘bhai’ (elder brother) and female ‘baji’ (elder sister). As a result, they perceive that they now have

---

3 Screen or veil
a close enough relationship “it is very common for people to become very friendly and ask very personal questions” and “they ask personal and intimate questions and also ask for personal numbers”.

v) Custom and Tradition (Gift giving and Hospitality)

Pakistanis are renowned for their generosity and their love and respect towards their guests. In Islam, a guest is a blessing from Allah. So, however poor people are, they will go out of their way to welcome their guests with open arms. They believe that this would please Allah. “I don’t know what foreigners do when they go for community field work but in our culture, they offer us tea, coffee, eggs, even seasonal fruits and many other gifts”. Also, “we have to take tea with them and have lunch when they offer us meal, to give them assurance that we belong with them and to win their trust”.

144
<table>
<thead>
<tr>
<th>No.</th>
<th>Themes</th>
<th>Key Messages</th>
</tr>
</thead>
</table>
| 1   | Religious principles and rules              | • Religious practices are a way of life in the Pakistani culture.  
• Prayer times should be respected, particularly Jummah (Friday) prayers. Men in particular go to the mosque to pray  
• Imams and other religious scholars are held in high esteem in their communities. Building rapport with these religious leaders would help |
| 2   | Concept of autonomy and privacy             | • The notion of ‘shared decision making’ translates into the whole family being involved in deciding on what care should be given to the patient.                                                               |
| 3   | Notion of respect and trust                 | • Segregation between genders is expected and respect for female family members, stems from the religious and traditional belief to protect the family  
• Strong family loyalties and ties are based on the religious belief that looking after one’s own comes over and above any other relationships. |
| 4   | Cultural differences (etiquette)            | • Making eye contact and shaking hands across genders and age have different meaning.                                                                                                                                 |
| 5   | Custom and tradition (gift giving and hospitality) | • Love and respect are expressed by giving gifts and offering food and drink to visitors.  
• Researchers from HIC may find this overwhelming. Saying no gently and politely would ensure people’s feelings are not hurt. |
5.3 Semi-structured interviews with clinicians

A semi structured topic guide (see appendix 2) was developed using the following steps.

- I first developed a list of broad, open ended questions with associated prompts reviewing the literature. These open-ended questions were designed in a way to draw out similar information from all interviewees but allowing the interviewee to frame their responses from their own unique perspectives.

- I and a clinical psychologist (MA) discussed my questions to make sure all topics were covered. We then compiled a first draft of the topic guide.

- The first draft of topic guide was sent to my supervisors for their comments and feedback. My 2nd supervisor, Dr Alexandra Pitman who is a psychiatrist with a special interest in bereavement and self-harm & suicide research and service development evaluated the topic guide for appropriateness of language and to make sure all relevant areas were included.

- The topic guide was also shared with expert qualitative researcher (TK) in Pakistan for her feedback.
The following themes and questions were covered in the topic guide:

**Table 8: Themes and questions in the topic guide for semi structured interviews**

<table>
<thead>
<tr>
<th>Themes</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipoise and Randomisation</td>
<td>1 What do you mean when you hear people talk about equipoise? (The Cochrane collaboration defines equipoise as “a state of uncertainty where a person believes it is equally likely that either of the two treatment options is better” (<a href="http://www.cochrane.org">www.cochrane.org</a>))</td>
</tr>
<tr>
<td></td>
<td>4 What could be the reasons for using randomisation for evaluation of psychological interventions against other treatments?</td>
</tr>
<tr>
<td></td>
<td>5 How comfortable are you with enrolling patients into RCTs that compare psychological intervention with no treatment? Would you feel more comfortable if the choice was between that treatment and some other treatment options?</td>
</tr>
<tr>
<td>2. Effectiveness of psychological therapies</td>
<td>6 What are your views about effectiveness of psychological treatments compared to drug treatment?</td>
</tr>
<tr>
<td></td>
<td>7 In your opinion is YCMAP plus TAU preferable to TAU alone for young patients?</td>
</tr>
<tr>
<td></td>
<td>8 Have you got a sense as to what the outcome of the trial will be?</td>
</tr>
</tbody>
</table>
### 3. Ethical Issues

9. What are the potential ethical issues that could arise while conducting the study?

10. What barriers should we consider while planning RCTs?

11. What could be the possible participant or his/her family’s reactions when asking to participate in RCTs?

### 4. Importance of RCTs comparing psychological inventions with other treatments

12. What are the needs, importance and scope of RCTs comparing psychological therapies with other treatments in our country?

13. What recommendations can you make for future efforts to evaluate psychological therapies for self harm in Pakistan?

### 5. Influencing policy

13. What is needed to persuade policy makers and funders, health professionals and participants to adopt psychological therapies instead of other treatments such that they become ‘standard of care’
The data was collected from February 2020 till December 202. Using the topic guide, semi structured interviews were conducted by myself with 20 clinicians from three trial sites. There were five participants from Lahore, six from Rawalpindi and nine from Karachi. These were psychiatrists, GPs, and Emergency Care doctors. 8 were female and 12 were male. All 20 clinicians volunteered to take part in the interviews. Three opportunistic interviews were also conducted with three members of the National Assembly. The participants were invited to respond in Urdu, English or Urdu/English mixed which ever language they felt comfortable in as I am proficient in both Urdu and English. I travelled to Pakistan to conduct the interviews. Interviews in Lahore and Rawalpindi were face to face, but I had to return back to the UK abruptly due to the Corona Virus Pandemic. All nine Karachi interviews were conducted online. For interviewees online, I added a question to find out about their experience of on line interview. All responded positively and most of them said they were very comfortable and even forgot that the interview was not face to face. Some even preferred being interviewed online as they felt they could choose a place where they could be interviewed in privacy and without interruptions.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinicians involved in the trial</th>
<th>Clinicians not involved in the trial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean 47.77 years</td>
<td>Mean 50.09 years</td>
<td>Mean 48.93 years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Department</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>GP</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Ward doctor</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karachi</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Lahore</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Rawalpindi</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
Remote Research Method

In my study, the use of remote research method was more by necessity than design. It has its advantages as it can be more efficient as logistically it is feasible to hold more interviews in one day. Also, it is budget friendly from the point of view of not requiring travel costs and finally as I found in my Focus Group Discussion, geographically it is feasible to include participants from multiple locations which enriches the discussion and consequently widens the diversity of data collected.

Data were analysed using Braun and Clarke’s reflexive thematic analysis approach (2019), which involved:

Familiarisation:

From the interview recordings, the data was transcribed and translated by myself. This gave me the opportunity to engage with the data. Following translation, the data was sent to a bilingual qualitative researcher at PILL to validate the translations.

Coding (organic and subjective):

I coded the data using the one coder process. I immersed myself in the data by listening to the recordings several times and subjectively broke down the participant responses and stories so core category and related concepts emerged organically. For cross reliability purposes the data was also coded by a bilingual qualitative researcher (MA) at PILL using the topic guide. The purpose for using the ‘code book’ topic guide coding was to capture all the topics covered in the interviews. The code book analysis was conducted by qualitative researcher (ST) at PILL following Braun and Clarke’s 6 Step Thematic Analysis Framework (2006).
The coder followed five of the six steps. Which are:

1. Familiarise yourself with your data.
2. Assign preliminary codes to your data in order to describe the content.
3. Search for patterns or themes in your codes across the different interviews.
4. Review themes.
5. Define and name themes.

**Produce your report** This step was omitted to allow me to write up a compelling ‘story’ based on my own analysis, reflections and refinement of the data in order to present a coherent argument to answer my research questions.

This collaboration in coding allowed the same data to be examined from different viewpoints. It also provided an opportunity for me to reflect on codes and theme development.

**Theme development (review initial themes against coded data and entire data set; subjective and interpretive):**

I developed initial themes by reflecting on the initial concepts that I interpreted from the views, perceptions and experiences of the clinicians. I further refined the themes in relation to their perceptions of efficacy or inefficacy of the psychological interventions as well as prior beliefs and cultural, religious and social values of the clinicians.

To add rigour to the thematic analytical process, a further step was added. The thematic analysis was scrutinised and validated by PILL Qualitative Research Group.
Qualitative Research Findings

5.4 Results from clinicians’ semi structured interviews

Three main themes evolved from the semi structured interviews with the clinicians:

1 Clinical equipoise as moral justification for RCTs

The interviews revealed that almost all clinicians were unfamiliar with the concept of equipoise. However, they wholeheartedly believed that randomisation was essential to reduce bias and there was the need to conduct RCTs for Evidence Based Medicine (EBM). Although, this clinician was not unaccustomed by the terminology of clinical equipoise, their statement provides the justification of the concept. “Obviously to overcome subjectivity so that subjectivity/biasness may not intervene in any aspects of the study. Like for an instance, we randomise with respect to age, education, or any other so that there remains no chance of subjectivity.” (Lhr Int 2, Line no 26 to 28 – Dr A, male, 49 yrs, GP)

There was overwhelming consensus that randomisation rules out and equally balances preferences. One interviewee said talking about RCTs “It is to eliminate the chance of biasness or to avoid the personal judgement” (Pnd - Int 03, Line no. 43 – Dr D, female, 33 yrs, Emergency department).

There was unfamiliarity with equipoise as a term but when talking about randomisation and the need to eliminate bias, the clinicians gave the moral justification which describes the concept of equipoise. As one clinician said,” when we are not sure which therapy is more beneficial for the patient and which is not? What might be the results of that therapy? So you need a randomised trial to get to know which one is better” (Lhr - Int 05, Line no. 7-9 – Dr C, male, 42 yrs, Psychiatrist).

Clinicians expressed a desire to generate ‘home grown’ evidence base as the perception is that most research is conducted in the global North and therefore not culturally relevant to the context of Pakistan.
One clinician alluded that “we have to realise that when you are looking at evidence, evidence for everything is being taken from the West. How do we know that it fits into our cultural context? How do we know it is fitting into our religious context? How do we know that it is able to meet the challenges of both the geographical, religious, psychosocial, personal, emotional, family circumstances of Pakistan? How will these challenges be overcome?” (Khi - Int 07, Line no. 428-432 – Dr N, male, 61 yrs, Psychiatrist). Most clinicians said there was a need for more evidence base from LMICs such as Pakistan. According to one clinician, “there is a beautiful and a very relevant systematic review of systematic reviews done where they have looked at all the SDGs and social determinants and that there are a number of countries that have been included in that systematic review but none of the studies from Pakistan were included in that systematic review because there aren’t enough reviews or studies so we have to develop local research data and evidence base so we can be informed as to what works and what doesn’t work for our population” (Khi - Int 08 Line no. 380-385 – Dr O, female, 60 yrs, Psychiatrist).

The analysis of the views deduce that clinicians regard clinical equipoise as an ethical justification for conducting RCTs and RCTs to be the best practice to gather most accurate and rigorous evidence base. As one clinician said (talking about RCT), “yes this is a good method. You are not putting the patient using your own choices or driving the results towards your choices rather it is random, anybody can check the efficacy and it is not in the knowledge that whether the patient will respond or not or whether it will work or not” (Lhr - Int 05, Line no 13-16 - Dr C, male, 42 years, Psychiatrist).

And the quote below from a clinician sums it up well.

“The main concern of a researcher is from the ethical aspects, and equipoise will provide us with the ethical grounds and justification to conduct the trial. The more the clinicians as a community will be
uncertain, the more credible and robust it becomes.” (Pnd - Int 06, Line no, 23-25 – Dr E, male, 52 yrs, Psychiatrist). Although clinicians did not appear to have come across the notion of equipoise, the preceding comment demonstrates that they regarded clinical equipoise as moral and ethical justification for conducting RCTs.

Most clinicians concurred that psychological interventions were an effective treatment for self-harm and suicide prevention. They said that in certain cases, a combination of pharmacological as well as psychological interventions may be required initially but they deemed psychological therapies to be the best particularly in young people. In adolescence, issues such as interpersonal relationships, internalising stress, attitudinal and behavioural problems and the likelihood to succumb to peer and social pressures easily can be huge stressors in these formative years resulting in self-harming behaviour. Talking therapies in these cases are of great help. One clinician stated, “we are doing this psychological therapy with treatment as usual. I believe that this would be very helpful because firstly in the young people these days, the biggest problem with them is that they don’t show compliance with the drug treatment. What they want to do is share their problems, they feel they are not heard and psychological therapy will help with that. When the patient has someone to talk to they want to share their problem with and talk to someone who is an expert in this field and who knows how to conduct discussions on something that can help the patients it can be a kind of conversation that will help patients to understand their problems, understanding their disease and managing it so even if the drug treatment is considered secondary”. They went on to say “I think the basic thing that young people need is psychological treatment and on top of that we can give drug treatment if needed but no drug treatment would be effective if there wasn't any psychological treatment so I believe that YCMAP would be extremely beneficial given along with drug treatment if the drug treatment is necessary” (Pnd Int 04, line no 177-188, Dr F, male, 36 yrs, Psychiatrist).
Another said, “In my experience I have got good outcomes and results from psychotherapy”. (Khi - Int 05, Line no. 252 – Dr P, male, 31 yrs, GP)

A few clinicians’ opinion was that psychological interventions are proving to be effective in psychosis as well and there are some studies to support that. However, the evidence is not entirely clear and there is a need to gather further evidence. One clinician mentioned “now we are getting evidence that even in psychosis, psychotherapy can work, even in auditory hallucinations but still we are collecting evidence for it some are clear but some are unclear” (Khi - Int 0 4, line no, 313 to 315 – Dr Q, male, 49 yrs, Psychiatrist).

Clinicians also supported psychological therapy as ‘early intervention’ to reduce the need for pharmacological intervention. There is a lot of evidence in high income countries on the effectiveness of cognitive behaviour therapy and talking therapies as early intervention in a lot of care pathways such as NICE guidelines. The statement by one clinician encapsulates the majority view.

“For majority of things, it’s always that the first option has to be psychosocial intervention. Pharmacological always has to be the last option.” (Khi - Int 07, Line no. 214-216 – Dr N, male, 61 yrs, Psychiatrist).

One clinician also touched on the global significance of YCMAP, they claimed “it will be helpful to people around the globe. Here we have some cultural things which might not be in UK, so when we will receive the data and we will be having reasons of self-harm that why people are doing this, because we have different religious aspects I think we will be able to address them and minimise them.” (Pnd int 05, line 164-167 – Dr G, male, 54 yrs, Psychiatrist)

Overall, there seemed to be a consensus on the effectiveness of psychological therapies, but good training of psychologists was an issue highlighted by clinicians. Training needs and lack of professionalism was an issue concerning most clinicians. One stated that, “a lot of universities are teaching psychology, but the study is mainly theoretical what they
learn from books, there is hardly any practical training so their (talking about psychologists) patient interaction is very less and you need experience of patient interaction, learning from patients and seeing them in hospital settings is different. They will learn psychological interventions, if they will get coaching and guidance, then they will see patients more proficiently. These things are lacking in our country.” (Pnd Int 05, line 88-92 – Dr G, male, 54 yrs, Psychiatrist)

Clinicians declared that YCMAP may produce good outcomes but it is important to have capable and competent psychologists to deliver the intervention to make it mainstream. Currently, clinicians believed there was a gap in capacity of good, trained psychologists and also lack of knowledge base and understanding of psychological tools in GPs and other clinicians. One clinician expressed, “In my experience, there are just one or two psychologists in Lahore who have proper testing services otherwise it just doesn’t exist. Psychology as a professional need to be professionalised. The training should be more transparent and they should be using evaluated tools. They are dealing with personality disorders, but they don’t have the tools to carry out the right tests, some of the tests are very expensive so there should be a library where psychologists can have access to these and for use on their patients and results are shared with patients. To be honest, only one or two psychologists are professional in my eyes while rest of them are sub-standard”. (Lhr Int 02, Line no 211- 219 – Dr A, male, 49, GP). This viewpoint came up over and over again. Clinicians also remarked on a lack of guidelines and where there were guidelines, there was a lack of training in implementation of such guidelines. One clinician said “I get in a quandary as to what to do in case of suicide? This is much more dangerous than HIV. So, I grapple with different issues; should we confine the patient or let them carry on with life but if one day they will decide to end their life, they will not stop. These are very difficult issues. (Lhr - Int 01, Line no. 371- 374 – Dr L, male, 59, Psychiatrist).

To sum up, there was a general acceptance of RCT as the scientific gold standard. Most clinicians were of the opinion that it was important to
conduct ‘home grown’ RCT e.g., YCMAP, despite their individual beliefs in talking therapies and irrespective of evidence elsewhere. However, there was consensus that there was an urgent need to professionalise psychology as a profession and for good psychological training for all health professionals.

2 Duties of care to individual patients

The clinicians were very aware of their duty of care when recruiting patients into clinical trials. Most clinicians supported clinical trials and recognised, that individual patients might be better off in the trial. This was because they believed that in an environment, where access to health care was scarce and in particular, for mental health conditions due to cultural, economic and social reasons, there may be no treatment as usual for the patients. So, recruitment in RCT would be in the best interest of their patients. Clinicians also recognised that RCTs provided intervention to patients albeit only to 50% but that was deemed better than none. One commented that “I will recruit the patient, as at the moment they are getting nothing so at least in the trial there will be a chance that they may receive CBT. (Lhr - Int 02, Line no. 54-55 – Dr A, male, 49 yrs, Psychiatrist). Another said “in a place like Pakistan even the control arm is better than no service” (Khi - Int 07, Line no.196 – Dr N, male, 61 yrs, Psychiatrist)

The benefit of recruiting a patient in a RCT was further substantiated by the clinicians. One said “even if there is no treatment it involves a whole process of consent, explaining, somebody going to visit them, having baselines done, screening done, follow ups. Those are the same. So, they have an opportunity of a professional, a clinician, a psychologist, a researcher spending an hour at times doing assessments with them. That in itself has therapeutic components to it”. (Khi - Int 08, Line no. 82-86 – Dr O, female, 60 yrs, Psychiatrist).

Although, in the context of conducting RCTs the clinicians have a dual role of doctor/investigator, it appeared from the interviews that the ethical principle of ‘duty of care’ and ‘do no harm’ underpinned by the
Hippocratic oath remained first and foremost at the time of recruiting patients in clinical trials. This was articulated by one clinician that “we have taken our Hippocratic oath that we should do whatever is best for patients”. (Pnd - Int 01, Line no. 244 – Dr H, male, 51 yrs, Psychiatrist)

The process of taking proper consent appeared to be an important consideration contained within duty of care to their patient/participant. As part of their ‘duty of care’ to their patients, clinicians referred to giving the patients adequate time in order to explain the clinical trial and to listen to any concerns or issues that the patient may have.

Some clinicians reported that cultural barriers as well as associated cultural issues that differentiate the genders are a cause of higher rate of self-harm in female in Pakistan. A few of the clinicians also alluded that more women rather than men are labelled by the families and communities as being possessed by a supernatural being due to families unwilling to accept mental health issues as an ailment.

The involvement and interference, of both immediate and extended family in wanting to know all about the patient and more so in the case of females came up as a major issue. This was a cause of stress to clinicians with regard to confidentiality and consent taking.

Concerning gender disparity, one clinician stated that “…. in a lot of family set-ups, girls are not treated as their brothers are and they are still deprived of education, they are still deprived of basic human rights like having the choice to marry the person they want “. (Khi - Int 09, Line no. 234-237- Dr R, female, 32 yrs, GP).

The impact of the patriarchal culture on consent giving and decision making was a narrative running across all interviews. Clinicians also reported that due to cultural and social norms of denial of mental illness, there was also secrecy by families when anyone self-harmed or attempted suicide, as it is perceived to be something to be ashamed about. Stigma, finger pointing attitudes of society with regards to mental illness, self-denial by the person and non-acceptability by family and the community at large is a huge barrier to accessing the scarce
mental health services. Most clinicians reported that due to stigma, there is secrecy and lack of acceptance of mental illness as an ailment. This results in delay in approaching the health services culminating in a crisis. Clinicians said often accessing mental health services is the last resort. A few clinicians mentioned that this cultural bias also exists amongst the clinicians themselves and often they are uncomfortable asking the patients about self-harm and that they may even skip over the issue.

With respect to ‘duty of care’ to their patients, some clinicians were perturbed and expressed helplessness around their patients’ basic human rights not being met. One clinician disclosed, “It’s tough, very tough. Somebody you want to enrol and their husband or their chaperone sort of refuses to bring them to and from the clinic. They don’t want to do that and you know that this is a genuine client who genuinely needs the therapy. Hmm, it engenders stress, tension as we are not able to practice as we would like to but you get attuned to that and you work through this thick lack of understanding I would say. But for the sake of the patient, we need to do that, we need to put different hats. Sometimes, I am a manager of the service and I give them the economics of it that this procedure will cost this much and how frequently we do that and other times I am just playing a friendly person who is encouraging them to take a jog or get exercise. So, there are different hats you have to wear. (Khi. Int. 001, line no 319-327- Dr S, male, 53 yrs, Psychiatrist) This was a cause of ‘moral distress’ in clinicians.

Lack of appropriate infrastructure to provide adequate care to patients was also raised as a concern. Talking about lack of confidentiality, due to inadequate infrastructure and surroundings for patient care, one clinician reported “if I say to you that when I do Out Patient Department (OPD), I do justice to my patient then I will be totally wrong. I will start OPD at 9 and finish at 2 or 2.30 and in that OPD I will see 50 plus patients. At that rate if I say I do justice to the patient, I am not right. We have a flow of patients, the numbers of people are very huge, not only here but all over Pakistan. In fact, things are better here as clinics
are separate. If you visit other places, you will find a big room where there will be a psychologist, consultant and GP, there will be a crowd of 40 patients and their attendants, the patient is telling you about himself and everyone may be listening. Now, in this situation where is the confidentiality and what ethics? (Pnd - Int 05, Line no. 214-220 – Dr G, male, 54 yrs, Psychiatrist)

Also, on confidentiality one clinician spoke of a general lack of awareness in people about their basic human rights saying, “People in our country, especially those from the lower class they don't understand the concept of confidentiality even in our OPD, when we are taking history of patients, there are many other patients around them sometimes. When they are giving the history, they don't understand that this is something they have a right to keep private if they want to. They don't even know if that is what they can avail, they don't understand it. So, confidentiality is a concept that is totally alien to them, they don't have a problem with that because they don't even realise it in the first place” (Lhr - Int 04, Line no 430 to 437 – Dr M, female, 41 yrs, Emergency department)

The role of the clinician as a protector of the patient both from the professional and religious perspective was considered of utmost importance. This is illustrated by a clinician’s comment, “Once I have seen somebody, my kind of ethical, moral, clinical, professional and religious commitment is with that individual”. (Khi - Int 07, Line no. 354-355 – Dr N, male, 61 yrs, Psychiatrist).

Religiosity is the golden thread that runs throughout the qualitative data. Most clinicians talked about sanctity of life and a blessing from Allah. There is this innate belief that religious therapy alongside psychotherapy would help prevent patients from self-harming and attempting suicide as Allah had sent human beings on this earth for a worthwhile purpose. It is interesting to note that although all clinicians who participated in this research were Muslims, the therapeutic conception of religion was not just for Islam but for all religions. Some
clinicians said that they actively ‘prescribed’ recitation of the Holy Quran, attending church or going to the mandir for meditation to their patients. They were also of the opinion that talking to the Almighty was consanguineous to ‘talking therapy’. One clinician stated that “the idea is not to convert people into religiosity but if they have a belief system, to use those entrenched resilience or stress coping strategies to their advantage.” (Khi - Int 07, Line no. 228-230 – Dr N, male, 61 yrs, Psychiatrist

Most clinicians were of the view that using the patients’ belief model was a major component of their holistic psychosocial work and they encouraged the patients to continue to go to the faith healers but strictly advised the patients to continue with their medication and also not eat or drink any potions given by these healers. The clinicians considered this was in keeping with the social norms and beliefs of the patients. The concept of placebo and faith healers acting as placebo came up several times. One clinician talking about people using ‘pirs’ as first point of contact for mental health issues said, “they go to people like spiritual healers (Pir⁴)… who never give any medicine, who will only tell them to read this and to do this and that and people accept that, so…. if they accept that why won’t they accept psychotherapy…. Spiritual healers also do not give any medicine. They are neither physicians nor do they know about the pharmacology… But they have a very powerful placebo effect … These pirs are sitting on a mountain or at a very high place and to visit them people have to go bare footed; people say that while they are climbing the mountain their symptoms get better (laughing)”. (LHR – Int 01, Line no.142-148 – Dr L, male, 59 yrs, Psychiatrist)

Going to the faith healers and its effectiveness is an intrinsic belief and a conviction in the Pakistani culture, similar to a placebo effect engendering motivation and good results. A clinician stated that “Patients with paralysis and convulsions seem to get better when they visit these pirs. So, if pirs can be so effective…… why not

⁴ Muslim holy man
psychotherapy? You see, they don’t give any medicine… people know that he is not a doctor and will not prescribe any medicine but still there is a very good effect…, so similarly patients have to be told that there is treatment by talking and counselling…” (Lhr Int 01, Line no. 149-152 – Dr L, male, 59 yrs, Psychiatrist). Some clinicians themselves believed that it works and produces positive outcomes. One clinician asked me “Can I mention another treatment that they can get, may be you know some kind of faith healers, or may be going to some kind of Aalim? And they said “they (referring to the patients) presume it is doing good so what I would suggest to them not to stop going to the Aalim because it is all about psychology sometimes it may be just helping them or may be drug is helping them, we have the concept of placebo in our allopathic medicine, so that could be that faith healer or whatever that would be acting as a placebo” (Khi – Int 06, Line no. 146 – 151 – Dr T, female, 48 yrs, GP) Most clinicians were of the opinion that psychological as well as spiritual treatments were needed, particularly in the case of self-harm and suicide as there are lots of myths and misconceptions that may be the root cause here. Although the World Health Organization has included spiritual health and well-being as an aspect of health but spiritual interventions seem to be absent in care models.

Religiosity remains a common train of thought. Faith healers, religious imams and pirs are held in high esteem in the predominantly Islamic culture of Pakistan. Most clinicians inferred that the masjid imam’s sermon constituted to be the last word for people and was followed unquestioningly. This was underpinned by rapport and trust of the faith healers which consequently resulted in powerful placebo effect. Most clinicians supported the idea of engaging and involving religious leaders and faith healers as the masjid is the focal point of the community and the imam plays a pivotal role in providing guidance. A few clinicians cited the example of their collaborative work with pirs and shrines. Although, there was support of the ‘pir model’, some clinicians

\footnote{Scholar}
saw a barrier in people’s belief model of seeking faith healers as a first point of contact. According to one clinician, “In most of the families, they are following Pirs (faith healers) blindly just because their forefathers used to follow them. If they are born a Muslim, they are a Muslim. They will not question. Even in this 21st century, there is a shrine here where the cure for neonatal jaundice is given to people which is to bury the baby’s head in the sand for three days and that will cure the jaundice. (Khi – Int. 02, line no 254-258 – Dr U, male, 38 yrs, Emergency department)

The religious belief that someone is possessed by the ‘jinn’ is also a barrier and a challenge for timely medical and psychological intervention. The cultural and religious indoctrination of ‘jinn’ or ‘saya hai’ (possessed by spirit or ghost) is not limited to the lower socio-economical classes but also part of the belief system of the educated classes. Most people come to the doctor as a last resort which causes significant delay in treatment.

Stigma and the concept of a shame-based culture came up in all interview responses. Phrases like ‘men don’t cry’, ‘mental illness is a taboo’, stigmatisation, labelling and ‘being judgemental’ prevailing in society were mentioned over and over again. Also, clinicians said that as going to a psychiatrist was not acceptable, conversion disorder was very prevalent in particular amongst women whose entry into the health services would be through complaining of back ache or pain in the joints as this was more acceptable by the society in Pakistan. Clinicians remarked that in families where women have to preserve ‘pardah’, they were not allowed to attend the health services due to religious reasons.

Suicide in considered haram in the Pakistani Muslim religion and culture. It is also a criminal act to self-harm and attempt suicide. Most clinicians said that people are ashamed of their suicidal ideations and do not come forward due to the fear of being shunned by their communities and society at large. Clinicians also mentioned that
families are afraid of police involvement and risk of becoming a victim of police bribery. One clinician stated, “…then the legal aspect of it as self-harm and attempting suicide is a criminal act. Because it has to be reported if somebody has attempted suicide, there is police involvement and then there is corruption in that because people don’t want it to be a police case. A lot of time, there is bribery involved, people don’t have that kind of money. So, they don’t report these cases and they don’t seek help.” (Lhr – Int 01, Line 305-308 – Dr L, male, 59 yrs, Psychiatrist)

A few clinicians reported that most cases of self-harm and overdoses went unreported by the clinicians for these reasons. Clinicians just treated and counselled the patients as for them, saving their patient came first and foremost. “Suicide is considered haram in our culture and religion and people therefore feel shy and ashamed about their suicidal ideation that they feel like ending their life. When I was working in hospital, I saw many young girls of age 16, 17 or 18 taking overdose of benzodiazepines to attempt suicide. Although, according to the law I was supposed to inform the police before stomach wash but I used to just do it and scold these youngsters and pacified their parents.” (Lhr Int 05, Line 80-84 – Dr C, male, 42 yrs, Psychiatrist)

Clinicians reported that the religious belief of suicide being ‘haram’ and therefore the stigma around suicide in Pakistani society was a great barrier to accessing mental health services and this was not only in Muslims but also in people following other religions. This belief was also a reason for people with suicidal ideations for not seeking help and getting timely treatment. One clinician described it as “the person who is having suicidal thoughts and thoughts of self-harm, he does not think of himself as a patient, he thinks of himself as a sinner.” (Khi - Int 09, Line no. 399-400- Dr R, female, 32 yrs, GP)

In summary, clinicians recognise that individual patients might be better off in RCT hence recruitment was in their best interest. Clinicians proclaimed that ‘prescribing’ visits to faith healer was the promotion of
the psycho/socio/spiritual model which was also good for their patients religious well-being. Religious therapy was favoured as a complimentary therapy by most clinicians and they acknowledged using it ‘as treatment as usual’. Ostensibly, most clinicians accepted values relating to individual consent and confidentiality but there is an apparent tension with the collectivist, patriarchal and religious culture.

**Other Ethical Dilemmas**

Most clinicians highlighted the cultural, religious and social aspect of the conservative society as a hindrance to women accessing help. Even when families accepted that health care was required, clinicians reported that there were issues of confidentiality and privacy and issues of women being allowed to consult the doctor in privacy. It was also mentioned that some females used escapist tactics and behaviours of mental illness to gain psychiatric admission in order to escape dysfunctional domestic environment.

Some clinicians stated that the overall stigma of mental health impacted women further as when a female was labelled as having mental health issues they were typecast by the community as ‘pagal’ (mad). Clinicians further stated that “in the lower socio-economic classes due to financial reasons as well as being a male dominated society, women mostly do not express themselves for these reasons”.

(Lhr - Int 05, Line no. 256-257 – Dr C, male, 42 yrs, Psychiatrist). This creates further issues of accessibility and feelings of isolation and hopelessness in women. Most clinicians said that in our culture and society, the women are generally conditioned to look towards the elders and the male members of the family for decision taking. One clinician said that “I have noted that what happens is that, even if I ask the women and explain the whole concept to them, they do not feel comfortable in taking the decision on whether they are going to be involved in any studies or even when it comes to their personal procedures like for example surgical procedures. As I mentioned, if I

6 Lunatic
have to do an appendectomy of the patient and I have to take the consent from her, one of my patient said that she is not comfortable with giving consent herself and her husband will give it to me or her father would give. So, that’s what happens in our culture that women mostly look towards males in their family to give consent, who take decisions on their behalf.” (Pnd - Int 04, Line no 391 to 399 – Dr F, male, 36 yrs, Psychiatrist)

Clinicians were unanimous on the need to raise awareness about mental health issues. There was the need to educate the masses that when people have issues, it is not that they have been possessed or taken over by any supernatural being but that they were really suffering from an ailment which requires intervention and treatment. Clinicians mentioned using multiple modes of communication for awareness raising and educating the public and talked about a multi-pronged public health approach on reducing stigma. One clinician alluded that even when she herself needed psychological intervention, she did not know where to go to and who to approach. So there is also lack of awareness of availability of services, not only by the general public but also by the health professionals themselves. Clinicians stated that some of the means of raising awareness and reducing stigma would be engaging community and religious leaders, schools and colleges and using social media and television as channels of health promotion. Engaging policy makers by providing locally produced evidence base was also regarded as important to put pressure at policy level, both around decriminalising self-harm and suicide and also improving mental health care services. A few clinicians also suggested that it is important to educate the spiritual healers and include them in the mental health referral pathway so they would sign post patients into mental health care services.

Some clinicians raised concerns on the substandard quality of psychology training and lack of professionalism. They expressed the need for a regulatory and professional body for psychologists. The need for skill building and professionalism came up again and again.
Clinicians also intimated that there were moves by the profession and policy makers to regulate and professionalise. There were one or two examples of good practice particularly from Karachi. One clinician said that highly trained psychologists from abroad are returning to Pakistan. However, it was suggested that cultural adaptation of models of care would be beneficial in the context of Pakistan. Lack of infrastructure, scarcity of well-trained psychologists and culturally sensitive interventions to meet the needs of the population was a major concern from all clinicians.

The role of the family in the collectivist culture poses limitations towards individual autonomy in a society where interconnectedness is valued. However, the cultural, religious and social aspect of the conservative society is a hindrance particularly to women accessing help. There were issues of confidentiality and privacy and issues of women/girls not being allowed to consult the doctor in privacy. In addition, the societal denial towards mental health being an area requiring health care is a huge barrier. Also, self-harm and attempting suicide being a criminal offence is an immense hurdle to seeking help.

5.5 Conversations with Policy makers

Pakistan is in the process of developing its first mental health policy and implementation plan. This work is led by the Parliamentarian who is the lead on the UNAID SDGs. PILL had been invited by the Government to support this important policy development. The President of Pakistan hosted an All Parliamentary Mental Health Summit at the President House in March 2020.

As part of the PILL Team, I, the researcher had the opportunity to attend the Summit. This provided a fortuitous occasion to have informal interviews with three Members of the National Assembly (MNAs).

All three MNAs had a medical professional background. One was a paediatrician and the other two were psychologists.
psychologists is also the SDG lead and is championing change in legislation to decriminalise self-harm & suicide

The salient points from the conversations with the MNAs were that all three:

- favour RCTs to gather evidence base. However, locally gathered evidence base would convince them more.
- evidence base would help them convince others and champion legislative change.
- supportive of psychological interventions to be standard of care for some psychological conditions as part of the clinical care pathway
- favour culturally adapted interventions
- aware of the stigma of Mental Health and of the denial of mental health issues by families
- almost everyone in Pakistan turn to faith healers as a first point of contact on mental health issues
- engaging with religious leaders and to promote the need to seek clinical therapy as well as continue with ‘Dua’

It was remarkable to note that one policy maker was unaware of the high rates of suicide in Pakistan and in particular the high rates in young people.

5.6 Summary of research findings

To summarise, the qualitative research revealed the role of the family in the collectivist culture poses limitations towards individual autonomy in a society where interconnectedness is valued. However, the cultural, religious and social aspect of the conservative society is a hindrance particularly to women accessing help. There were issues of confidentiality and privacy and issues of women/girls not being allowed to consult the doctor in privacy. In addition, the societal denial towards mental illness being an area requiring health care is a huge barrier.

7 Prayer
Also, self-harm and attempting suicide being a criminal offence is a major block to seeking help. The discussion group with researchers provided the insight into the contextual differences in conducting research in a different setting. Research such as YCMAP carried out in the cultural context of countries like Pakistan when funded by western donors such as MRC, stipulate guidelines based on western values of individual autonomy. However, cultural, religious and social patriarchal construct of Pakistani society give rise to challenges and tensions on individual autonomy and informed consent as prescribed by western bio-ethical doctrine of autonomous decision making. In the case of participants and their guardians who may not be literate, informed consent can be problematic. The survey overwhelmingly suggest that the clinicians regard the need for randomisation as essential to reduce bias. However, for example, in YCMAP, clinicians were required to summerise the study information to recruit the participants (Husain et al 2021). The corollary of this process is the risk of introduction of clinician bias.

On the contrary, for some clinicians their own beliefs and moral obligations towards their patient have been in discord with societal construct of rules on autonomy and decision making in Pakistan resulting in ‘moral injury’ – having to perform against what the professionals morally believe is right (Best, 2021)

Pre-eminence of spiritual guidance and ‘treatment as usual’ may mean patients, often female, delay or are denied professional help. Although, clinicians in general are supportive of religious therapy but they draw the line at supporting potions prescribed by faith healers. Some clinicians find inability to respect individual rights difficult or distressing and may resort to distracting tactics towards the family to protect patients’ individual rights. Regardless of certain tensions, there is overall acceptance by clinicians that family values are best even for
females. The need for awareness and training on rights and mental health issues was acknowledged by all.

5.7 The Researchers’ Reflections

My research is based on exploring the concept of equipoise in the cultural setting of Pakistan. My motivation for investigating the concept of equipoise was because I have been working with PILL researchers for several years on RCTs so intuitively I became interested in the ethical underpinning of conducting RCTs. Initially, my inquiry was purely academic i.e., reading and literature search on the history, ethical notion, and the technical aspects of the topic. This, I found interesting albeit rather bland. As the research progressed and I began my qualitative research, my personal narrative of connecting to my roots came into play. The semi structured interviews provided opportunity to delve into the personal and professional accounts of the experiences of the clinicians which evoked fascination and curiosity. Although, hardly any clinician was aware of ‘equipoise’ as a terminology. However, there was a general consensus on the need for randomisation to eliminate bias and uncertainty and the necessity for scientific evidence base. The conversation moved on to the environmental, cultural, religious, and social context of Pakistan. The issues uncovered progressed from lack of infrastructure and the ethical implications of working in unfit premises resulting in breaches of confidentiality, dignity and privacy causing moral distress to clinicians on to societal ethical issues of stigma and shame of mental health issues.

Conducting research in my ‘native’ country provided both opportunities and challenges. Being of Pakistani heritage undoubtedly had an influence at all levels of research and the underlying cultural identity may have engendered assumptions that may have brought in my personal biases into the interpretations. My Pakistani heritage and my Islamic background formed a golden thread connecting women’s issues into my own cultural framework. My positionality as an insider/outsider meant that I did not have a full understanding of the
ground reality so some of the narrative did not resonate with my personal experience. However, the wider issues described by the interviewees, my cultural, gender-based and religious affiliations as well as the focus group discussions provided the knowledge. According to Burr, 2018, the researcher cannot and (do not intend to be ‘objective’ and ones’ own biases and social influences) impact on the interpretation of findings. That is why it was important to revisit the texts and cross validate as described in the thematic analysis section above.
Chapter 6: Discussion

6.1 Summary of results

My thesis examined the main conceptions of equipoise and applied them in cultural context of Pakistan. It delved into how cultural, moral and religious values relate to western concepts of research ethics and undertook to investigate specific research questions related to the YCMAP RCT. Moreover, I compared YCMAP with the South African case law to demonstrate the RCT’s wider effort to support young peoples’ human right to health in Pakistan. In order, to demonstrate that CMAP study for adults was not externally valid for young people, I examined the anthropological, physio-psychological differences in the characteristics of children and adults and their human development. The different research instruments and methods employed to examine the research questions and triangulation of data added context and validity to the research findings and this mode of investigation provided further rigour and robustness to the conclusions. As far as I am aware this is the first research study of its kind to examine the ethical imperatives of conducting RCTs in a different cultural context and the influences of cultural, moral, religious and social confounders that impact medical research and practice in those settings.

The data from the survey helped to inform the issue of which conception of equipoise is morally appropriate for Y-CMAP. The majority (89.3%) of clinicians considered Y-CMAP as an effective treatment for young patients at risk of self-harm or suicide before the trial. However, there was a higher percentage of clinicians (87.5%) not involved in YCMAP as compared to 48.5% recruiting to the trial, who stated that there may be other treatments that may be equally good for the patients. Although, there was acknowledgement of individual treatment preferences, there was consensus on the need to conduct an RCT for reaching an evidence-based decision. This was specifically due to the reason to reduce bias. This suggests that there seems to be
enough evidence of uncertainty and the existence of clinical equipoise as moral justification of conducting the randomised clinical trial. Individual level or theoretical equipoise was not considered ethically necessary.

**Is clinical equipoise ‘fit for purpose’ for new trial designs?**

More recently, there is resurgence of interest and debate on the concept of equipoise especially with the rise of innovative trial designs (Hey et al., 2017).

With emergence of new trial designs such as umbrella trials which tests multiple interventions on a patient with single morbidity, basket trials to test new drugs in oncology patients, enrichment trials for precision medications aiming to boost efficiency by customising patient treatments who would benefit from bioinformatics factors, platform trials with multiple therapies and when one treatment is completed, a new treatment is introduced and cluster randomised trials where groups of participants are randomised. According to European Federation of Pharmaceutical Industries and Associations (EFPIA) Taskforce, 2020 clinical trial innovation is also enhancing efficiency by developing standardised protocols, and templates to include patient centred metrics such as Patient Reported Outcome Measures (PROMS). Considering these developments, scientists are questioning whether the concept of equipoise is fit for purpose for these new trial design innovations. Hays and Colleagues (2018) suggest clinical equipoise needs to adapt. Acknowledging that equipoise remains an important principle for the moral justification of clinical trials, they propose that more explicit guidelines for the assessment of uncertainty are needed with the goal of providing transparency and clarity on uncertainties and risks, for the benefit of both researchers and participants. Tristan et al 2022, argue that clinical equipoise poses a dilemma when trialling new therapeutics in sinister conditions such as biliary cancer. The heuristic would demand to provide the best possible treatment to the patient so the inherent will and desire of the clinician to do the best for their
patient could prove to be frustrating. They call for newer ways so that the duration as well as the size of the trial is shortened for the patient to be offered the best available treatment but at the same time clinical equipoise is not disrupted. On the other hand they accept that the ethical rigour to produce evidence based medicine and to maintain clinical equipoise deems it necessary that the outcomes are objective and scientifically robust, underpinned by the bioethical principles of beneficence and non-maleficence fulfilling the human values as physicians, carers and researchers.

RCTs although considered gold standard, however as the parameters of the trial design and conduct are set before patient recruitment and remain constant throughout the trial, there remains the uncertainty on whether the experimental treatment administered is providing the maximum benefit. (Legocki et al, 2015). Woodbury et al (2009) propose the new approach of Adaptive Clinical Trials (ACT) which would take advantage of the accumulating data and modify the parameters according to predefined criteria to reduce error and add value. According to Legocki et al (2015), few ACT designs are conducted due to limited experience and knowledge of ACT of the clinical triallists. The proponents of the new trial designs are advocating a more streamlined research process. The core element of these approaches is Response Adaptive Randomisation (RAR) The general consensus is that, for two-armed trials RAR has proved to be less efficient then the balance Fixed Randomisation Allocation (FRA) (London, 2017). RAR, on the other hand appears to have more favourable features for the newer trial designs. However, there is criticism that RAR violates the fundamental principle of equipoise as the notion of uncertainty is disrupted. This concern also gives rise to the question of ethical challenges that may result due to integration of research and treatment activities as RAR proposes.

As response-adaptive cross over trial design utilises the outcome data to move patient into the most effective treatment arm, the patient’s
exposure to the inferior arm is reduced and as a consequence, minimises the risk to the patient. This approach poses different ethical nuances and could be viewed as more beneficial to the individual patient (Legocki et al, 2015) and therefore could be justified, even though there would be lack of equipoise, if there would be a risk that the patient would be denied treatment by remaining in the inferior arm and where no other treatment exists. However, it has to be pointed out that this is not without limitations e.g. great vigilance on the part of investigators would be required, to ensure that the cross over process is adhered to, to avoid patients remaining on the non-responsive therapy and as a result coming to harm. A great risk to the trial itself would be the reduction of data at the latter part of the trial due to enhanced crossover or patient drop out. Additionally, it could be argued that there is potential of injustice in this approach as those patients recruited later would benefit from better treatment than those enrolled earlier in the trial.

Academics favouring the RAR component suggest that maintaining FRA throughout the course of the study is not for the welfare of the participants. They argue that updating the randomisation allocation to RAR would allow participants to benefit from the better performing intervention. Hence, this would be more ethically attractive as it results in the individual participants’ welfare. Some critics however argue that there is a tension between the RAR and clinical equipoise, as adjustment of allocation during the trial period would disturb clinical equipoise. As mentioned earlier, in addition to accumulation of data London’s point of view is that if all interventions at the beginning of the trial, are judged ‘best for the patient’ and viewed not to violate the welfare concern towards the patient by a set of experts, then clinical equipoise remains. London defends his viewpoint on the rationale that when participants are moved to the more favourable intervention, then all participants will still receive an intervention regarded as ‘best for the patient’ by a set of clinical experts. London favours this approach by suggesting that the trial provides an opportunity to clarify the relative
benefits of those interventions that have a ‘strong prima facie claim to social value’ (London, 2017). The German sociologist Max Weber developed the Theory of Social Stratification (Weber, M, 2010) based on socioeconomic factors. According to Jain P et al (2019), social value as described from Weberian point of view consists of nine key contributors i.e. cultural, economical, environmental, ethical, intellectual, physical, political, religious and social. Thus, it is assumed that changes in the lives of people manifested on these considerations and employed at grassroots level ensures resources both human and other materials are not misused but brings about real change for the benefit of the society. Consequently, London (2017) proclaims that the trial in itself is an essential step in reducing variation in clinical practice and thus improving care for the patients.

Trusting the views of experts is all well and good but according to Schunemann et al. (2019) the whole process of development of guidelines is flawed. Expert opinion on evidence based guidelines should be underpinned by factual evidence rather than the opinion of a group of experts; be they in the field of medicine, public health, patients, patients’ representatives or others. Sometimes, particularly in the case of rare diseases where there may be little data available, expert opinion based on first-hand knowledge may be the only source of information. This can be challenging. At times, expert opinion can get taken as expert evidence which has implications for the robustness of guidelines. For that reason, when developing guidelines, it is crucial to distinguish between ‘expert evidence’ and ‘expert opinion’ (Schunemann et al., 2019). Hence, Schunemann et al recommend that there needs to be a rigorous process to ensure it is ‘expert evidence’ that is being collected and not ‘expert opinion’. In meetings, when experts are expressing their opinions, there is a risk of opinion being taken as evidence. This is problematic as opinions, as well as not being supported by facts, are influenced by many other factors. These could be conflict of interest such as financial gains and/or other biases e.g. benefit for their own or their institutions research projects. There
could even be non-malign reasons such as memory bias. All these challenges would have impact on the credibility and integrity of the guidelines.

The inherent risk of bias and conflict of interest, the causal inference that there could be ambiguity between ‘expert evidence’ and ‘expert opinion’ at the time of developing guidelines is problematic with a high potential to disrupt clinical equipoise. Schunemann et al. (2019) suggest one way of solving this problem is to have systematic and transparent processes similar to the ones used in gathering research evidence.

There is general consensus amongst health scientists that RCTs are the most rigorous method for testing new treatments and it is also generally accepted that human subject experiments pose ethical issues (Ashcroft 2001). As discussed before, random allocation in RCTs is not well understood by patients and therefore can be a cause of concern to some patients. Ashcroft suggest some of these objections could have an underlying systematic basis, and may be due to cultural, religious, philosophical, or political beliefs.

**Why the concept of clinical equipoise may be considered differently in Pakistan?**

Part 8, Research Ethics and Consent, section 43 of Code of Ethics of Practice for Medical and Dental Practitioners, Regulations, Pakistan 2011 clearly states that “In any clinical trial there must be genuine uncertainty as to which treatment arm offers the most benefit”. However, the concept of equipoise can be problematic in more traditional cultures such as Pakistan, where the doctor/patients relationship may not be as egalitarian as in HICs (Lilford and Stevens 2001), and consequently patients would have difficulty in respecting or trusting a doctor who comes across as less knowledgeable (Ishiwata 1994) Where patients’ assumption is that doctor knows best particularly in cultures, where there is an expectation of authority and patriarchy in
the doctor/patient status. In such cultures equipoise can be perceived as incompetence on the part of the doctor. Additionally, as revealed from the clinicians’ interviews and the focus group discussion, the role of religion in the Islamic Republic of Pakistan plays a central role and is the ethical underpinning of many social functions. As discussed in Chapter 3 beneficence, non-maleficence, protection, and justice are all embedded in the religious scripture and thought of Islam. Although, it is problematic to tease out tradition, practices and behaviour form the cultural base, religion seems to dominate. Consequently, the values seem to stem from the religious teachings. From the interviews with the clinicians, it appeared that as clinicians and as recruiters of participants in RCTs, their clinical practice seemed to be influenced by their belief systems. This innate predominance of the value-base of the ‘protector role’ unknowingly introduce bias and have an impact on their recruitment decision making. The western clinical research rules are very prescriptive and specific for the individual and for the profession. These can create grounds for ‘medico-cultural’ conflict if transposed on other cultures with different religious and philosophical beliefs and traditions. (Unschuld 1975). Johnson’s (1992) research into Asian medical traditions (Ayurveda and Traditional Chinese Medicine) reveals that although ethics were mainly concerned with principles of behaviour for the profession, these ethical precepts were underpinned by humaneness and compassion. Codes of ethics are necessary to protect vulnerable research subjects. It is important to remain mindful in the moral interpretation of rules that whether what is required to be done to participants, is in reality, something we would wish to be done to us or our loved ones. Arthur Kleinman, psychiatrist and anthropologist, argues that in developing countries clinical research must be contextualised within the everyday beliefs, values and power dynamics. Often unrecognised by western clinical researchers, the differences in conceptions and expectations and norms can create conflict. As more and more western medical research is being done in non-western settings, it becomes an ethical exigent to study the local
impact and perceptions of this exogenous interaction with the indigenous medical research practices.

The fundamental difference between the western epistemology and the non-western contemporary medical systems has to be acknowledged (Johnson 1992).

The lack of communication skills of researchers and providers can be problematic from the point of view of patients fully understanding the risks. A focus on training is required both for the clinicians and research staff as well as for the patients. The need for professionalising psychology, improving the standards of training professionally as well as with regards to soft skills such as good communication skills was highlighted by almost all clinicians. Better trained doctors and researchers would be more confident and competent in providing neutral information to patients at the time of recruitment, thus maintaining clinical equipoise and without suggesting which randomisation allocation would be more efficient, in which trial design and when?

A secondary analysis of Shekhani’s scoping review (2018) identified that there was a gap on available literature on suicide prevention programmes in Pakistan. Clinicians’ interviewed substantiated this finding. “We need more robust evidence that is more relevant to our culture, that’s relevant to our people because there is evidence. There are a lot of RCTs done across the globe but none or very few in Pakistan so how would we know what works best in Pakistan amongst 10 different psychological interventions unless we have had an RCT for each of them” (Khi Int 8, pgs 371-374, Dr O, female, 60 yrs, Psychiatrist). Research group conducting the YCMAP trial had successfully conducted the CMAP study on which YCMAP is predicated upon. One may wonder why the need for YCMAP? The accumulation of data, when CMAP had already demonstrated positive outcomes could have been problematic from the perspective of disrupting equipoise. One clinician expressed the requirement to produce the evidence base as an ethical dilemma, “I think one of the ethical issues is the dilemma; knowing this is efficacious
treatment. So the ethical dilemma is now even more that, why can’t we have an open label and offer this to all as we know more now and it is not an unknown entity. In a population of slightly older age group, it’s been very efficacious so now to hold it back for the study to end becomes even more difficult, even bigger challenge but we still have to go through this hoop to provide robust gold standard data” (Khi Int 7, line 322-326, Dr N, male, 61 yrs Psychiatrist). However, as discussed in the ‘right to health’ chapter, it is evident that there are key differing characteristics between children and adults from the perspective of physio-psychological and behavioural and human development. Nearly 200 potential participants for the CMAP study had to be excluded due their age. They requested for a study for young people. More importantly, research guidance internationally is advocating more research with children and adolescents to build evidence base. (CIOMS 2016). Results of Hawthorn et al’s systematic review also concluded that there were no trials published on psychosocial and pharmacological interventions for prevention of self-harm in children and adolescents from LMICs. An imperative for conducting research in children and adolescents is predicated on the evidence of current practice of ‘off label’ and unlicensed drugs in children and young people which can have a potential of harm towards them. Furthermore, according to Smyth (2001), there are risks in depending on information from trials on adults as well as methodological issues when applying to children.

Increasingly, more and more guidance is advocating including the views of young people in research which is beginning to happen in HICs. However, according to Marsh et al, 2019, the need is more in low- and middle-income settings as there is a higher burden of disease and therefore a greater need for research. The intervention YCMAP was culturally adapted and modified for young people. The RCT has a youth advisory group and it is planned to do a ‘lessons learned’ discussion with the participants.
The above discourse provides a robust rationale for the YCMAP study and that the RCT did not violate the young people’s right to health at the same time. Additionally, the data from the community engagement and semi-structured interviews with clinicians provide an appreciation of the issues encountered by researchers in Pakistan. It fills a crucial knowledge gap regarding the cumulative and interactive effects of key potentially modifiable risk factors for self-harm and suicide in young Pakistanis. It is vital to shed light on these relationships since the potential for preventing adolescent self-harm and suicide by locally generated evidence base is significant. By adding this understanding to the impact of sociocultural differences and gender status within the Pakistan context, potential sources of inequality of access to health services for people of variable gender and socioeconomic origins will be clarified. Shekhani et al’s scoping review of the literature on self-harm in Pakistan also revealed that that there is more prevalence in young females. This was verified in the clinicians’ interviews. “Let’s suppose a girl says that I need to go out and educate myself but her parents will pressurise her and will not allow her to get education or to leave the house. So, she may start having symptoms but she will not be able to share. She may develop psychosis or start having suicidal thoughts or do self-harm. (Khi Int 2, pgs 87-91, Dr U, male, 48 yrs, Emergency department).”

The response to the two optional questions was 100%. The survey data from these voluntary questions revealed a high prevalence of self-harm and suicide in health professionals’ family and friends (27.9%) knew someone who had died with suicide and (32.4%) who knew someone, who had attempted suicide. This data suggests individual bias in qualitative results. Also, individual clinicians cited real examples, which suggest treatment preferences to be stronger. Thus, making the stance towards clinical equipoise as justification for RCTs even more robust.
The qualitative data culminated into the following ethical issues: 1) Religious misconception of act of suicide as 'haram' resulting in stigma, 2) Lack of awareness. Patients being taken to faith healers, perception of being possessed by 'jinn' resulting in delay in treatment, 3) Cultural construct that family knows best i.e. individual autonomy versus family decision making, 4) Moral conflict between ‘what’s best for my patients’ superseded by ‘family power dynamics and consent’.

It is interesting but not surprising to observe that religiosity was a golden thread across all the themes from the cultural analysis. The deeply ingrained religious and cultural convictions such as religious and spiritual therapy providing similar benefit and virtue makes Y-CMAP morally acceptable as well as the clinicians distinct religious and ethical duty to preserve life, since suicide is forbidden in Islam. Although the clinicians follow the biopsychological model, the conceptual framework they appear to be practicing seem to be based on religion and culture.

Most Islamic cultures share some common features such as interconnectedness and family loyalty, patriarchy and hierarchy both in social, political or moral authority as well as in age, conformity to norms of the collective i.e. societal over individual attitudes, goals and rights, resistance to cultural change and traditional values (Pridmore and Pasha, 2004). However, it is crucial to take into consideration that Muslims across the world do not approach Islam with the same perspective. Different sects such as Sunni, Shia and others have their own Islamic perspectives. Similarly, geographical and cultural aspects bring in variance in perspectives. Al Talib et al. (2019) in their study mapping Global Muslim Mental Health Research: analysis of trends in the English literature from 2000 to 2015, found that most research focused on the epidemiology and psychopathology rather than the religious or cultural aspects of the research subjects. They cautioned putting together all Muslims. Conflating all Muslims in one group would disregard the diversity of culture, norms and traditions. Furthermore, there is no one discipline of mental health in Islamic literature. Ibne
Sina in his book, The Canons of Medicine rejected the idea that mental illness is caused by evil spirits (jinns). Nevertheless, this view still persists in certain Islamic countries including Pakistan. Some believe mental illness to be a punishment from Alllah (Pridmore and Pasha, 2004). Beatings and exorcism continue as treatment for mental illness in some regions. This view prevails in Pakistan and most people believe that a person suffering from mental illness is possessed by demons. As one clinician stated “People believe that there is Jinn and its effects on the patients’ mind and behaviour and that it can be treated by faith healers”. (Pnd Int 6, line 163-164, Dr P, male, 39 yrs, GP)

From the community engagement exercise, there was recognition that at least in Pakistan, spiritual advice was often the first point of contact for patients rather than to clinicians. The trial was not designed to try to replace such religious norms but to work alongside them while recognising that there could be delays in referrals. There was also no restriction on accessing spiritual guidance making professional psychological therapies an addition not a substitute for such support. Importantly, mental health concerns are stigmatising and suicide a criminal offense. Working with religious leaders was therefore a critical part of community engagement with Y-CMAP and its evaluation through the RCT (submitted to BMJ Open). The concept of ‘dowa and dua’\(^8\), medicine and prayer going hand in hand as part of therapy tend to promote compliance and engagement. Thus, we can derive from this that Y-CMAP complement rather than compete with cultural norms especially, with the role of religion and spiritual guidance.

A number of key themes with regards to cultural differences, norms and values were also identified from the researchers’ discussion group including the role of religious principles and rules, issues related to autonomy and privacy, notion of respect and trust, cultural differences in terms of etiquette, and customs and traditions. These add validity to the data from the qualitative interviews.

\(^8\) Prayer and medicine
Evidence shows that involvement of religious leaders in raising awareness and community engagement is hugely important and they can play a significant role in bringing the community on-board even when addressing taboo topics (Raurk et al., 2019). Therefore, engaging with and empowering religious leaders through capacity building and offering them support, recognition and appreciation can be an important component of community engagement (Raurk et al., 2019). Similar findings have been highlighted through the discussion group where researchers strongly emphasised the role of respecting religious practices and involving religious leaders to strengthen community involvement and trust.
### Table 10: Summary of key results

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<tr>
<th>Research Question</th>
<th>Survey</th>
<th>FDG</th>
<th>SSI</th>
<th>Policy maker’s interviews</th>
<th>Assessment</th>
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<tr>
<td>Which intervention is preferable to the clinicians? YCMAP plus TAU compared to TAU only for young patients at risk of self-harm and suicide as measured by the responses of clinicians both involved in the trial and those not involved in the trial?</td>
<td>The majority (89.3%) of clinicians considered Y-CMAP as an effective treatment for young patients at risk of self-harm or suicide before the trial.</td>
<td>“We are doing psychological therapy with TAU I believe this will be very helpful”. “For majority of things, the first option must be psychological intervention. Pharmacological always must be the last option”</td>
<td>Supportive of culturally adapted psychological interventions to be standard of care for some psychological conditions</td>
<td>Agree (Survey, SSI, Policy makers’ interviews) Silent (FDG)</td>
<td></td>
</tr>
<tr>
<td>Whether there is uncertainty in clinicians to justify conducting Randomised Clinical Trial?</td>
<td>There was near consensus (90%) on the need to conduct an RCT for reaching an evidence-based decision. This was specifically due to the reason to reduce</td>
<td>“Randomisation is to eliminate the chance of biasness or to avoid the personal judgement” “when we are not sure which therapy is more beneficial for the patient and which is not, what might be the result of that therapy?”</td>
<td>Favour RCTs to gather evidence and that evidence base would help them convince others and champion legislative change</td>
<td>Agree (Survey, SSI, Policy makers’ interviews) Silent (FDG)</td>
<td></td>
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bias. This suggests that there seems to be enough evidence of uncertainty and the existence of clinical equipoise as moral justification of conducting the randomised clinical trial.

So, you need a randomised trial to get to know which one is better”. “The main concern of a researcher is from the ethical aspects and equipoise will provide us with the ethical grounds and justification to conduct the trial. The more the clinician as a community is uncertain, the more credible and robust it becomes”.

What are the potential cultural, moral, and religious barriers and potential ethical issues that need to be considered when planning RCTs in Pakistan?

The data from the discussion provided the insight into the culture of shared decision making, concept of “The women, even if they are able to understand and respond, the decision is taken by the males of their family. I have observed when it comes to consent in our culture”.

Aware of stigma of mental health and denial of mental health issues by families in Pakistan. Almost everyone in Pakistan turns to faith healers as first

Agree (FDG, SSI, Policy makers’ interviews)

Silent (Survey)
| What will be needed to persuade policy makers and funders, health professionals | autonomy and privacy, gender issues and notions of respect and trust | “I believe that every person has a right to decide about themselves, but this is not what happens here”. “Confidentiality is a concept that is totally alien to them but then we should guide them”. “The idea is not to convert people into religiosity, but if they have a belief system, to use those entrenched resilience or stress coping strategies to their advantage”. “They go to people like spiritual healers...” | point of contact on mental health issues. | Agree (SSI, Policy makers’ interviews) Silent (Survey, FDG) |
and participants to adopt psychological therapies to become standard care for young people who self-harm in Pakistan?

mental health issues and talked about a multi-pronged public health approach to reducing stigma. Engaging policy makers by providing locally gathered evidence base was also regarded as important to put pressure at policy level, both around decriminalisation of self-harm and suicide and improving mental health services. Clinicians also intimated that there were moves by the profession and policy makers to regulate and professionalise.

would convince them and help champion legislative change
6.2 Methodological Limitations

The research has some methodological as well as contextual limitations. Firstly, based on the Y-CMAP research teams’ experience with poor response to online surveys, questionnaires were physically taken to the health professionals. As a result, there was a 100% response rate. This may have introduced social desirability bias to the responses. Derived from the responses of the clinicians who were interviewed, hardly any of them were familiar with the concept of equipoise. Although, described at the beginning of the questionnaire and in the accompanying letter, these self-report questionnaires of the survey may have been subjected to lack of understanding of the concept of equipoise. As a lot of clinicians responded sometimes in English and sometimes in Urdu or in both, there is a risk that some information may have been lost in translation. Also, not being able to generalise acceptance of clinical equipoise from survey and interviews regarding one RCT is a limitation. The survey and interviews were conducted before recruitment and at very initial stage of recruitment to reduce preference bias of the trial intervention. However, there still may have been EBM bias of clinicians who are involved in recruiting patients to Y-CMAP rather than those treating patients routinely despite apparent demographic similarities between the groups in the study.

From the qualitative data, it is evident that the clinicians’ conviction towards their own belief systems had a direct impact on their practice. Although, the issue of autonomy and stigma towards women came up in almost all interviews, it seemed to be more dominant in female interviewee responses, this may have introduced some bias. The use of religious therapy as a parallel intervention to enhance treatment may introduce a placebo effect on patients’ participating in both arms of the trial. This may be a risk to the reliability and efficacy of the trial outcome. On the other hand, consideration of a persons’ religious and spiritual beliefs can provide a catalyst to recovery and help build engagement and rapport with the treatment model.
6.3 Implications and further areas of research

I, the researcher followed good research practice of confidentiality and informed consent. The participants were also explained about the safety and integrity of the data and that anonymity will be preserved at all times. In the interest of dissemination of new knowledge, the research findings will be shared in Pakistan and internationally through academic conferences, presentations, and publications nationally and internationally. In Pakistan, it is of particular importance to share this research on academic and medical platforms and with policy makers.

As this is the first study on the concept of equipoise in a LMIC. More research needs to take place in Pakistan and other LMIC to determine whether the concept of clinical equipoise is generally accepted as a moral justification for conducting RCTS. Also, psychological interventions may be deemed as low risk to participants therefore RCTs trialing other treatment interventions such as pharmacological and surgical would be an area of further research. Other areas of further research are put forward in the ‘recommendations’ section below.
Chapter 7: Conclusion

Based on these research findings, I infer that the clinical community in Pakistan regards RCTs, underpinned by the ethical framework of equipoise as a gold standard to develop home grown evidence base. However, it must be emphasised that there is an outstanding apparent tension which needs to be resolved between clinicians’ personal preference for psychological therapies and spiritual advice and acceptance of need for RCT on the basis of collective equipoise. The survey findings on the clinicians’ close association with someone either having attempted or committed suicide is alarming. It is to be reiterated that clinicians only needed to respond to these questions if they felt comfortable. Surprisingly, all clinicians responded. Further research needs to take place into the reasons for this. The data from the focus group and the community engagement process suggest that it is important to acknowledge and recognise the differences in cultural, moral, and religious beliefs and values of different societal constructs. Development of a cultural protocol for researchers would be a desirable step in fostering relationships between researchers from HIC and the communities they wish to recruit in research. In addition to accepted practices of community engagement and for special regard for protecting vulnerable cultures, observing a cultural protocol is another way in which researchers can show respect towards different cultural norms and values. A protocol would then become an integral part of the community and participatory engagement process.

Finally, clinical rather than theoretical equipoise in the West is still controversial, as illustrated by early access to medical products and COVID-19, and clearly not sufficient to be made culturally appropriate. Therefore, it would be culturally blind to transpose western individualistic, principle-based ethics into a society where culture and religion are so intertwined.
Chapter 8: Recommendations

1. When clinical equipoise was widely accepted standard for clinicians taking part in the YCMAP trial, despite having personal preferences for the intervention, those not involved in the trial stated that there would be other treatments that may be equally effective for young people who self-harm, suggesting they were more likely to be in individual equipoise. More work is needed to determine whether clinical equipoise is more generally accepted as the moral foundation for RCTs in Pakistan. The practice of assessing clinical equipoise needs to be an inclusive practice of soliciting treatment preferences and beliefs of the whole community of clinicians and not only those already involved in research, to consider the cultural aspects of different treatments more fully.

2. Data from the qualitative interviews further informed debates around perceived personal benefits of RCTs. From the participant benefit point of view on the merits of randomisation, Lilford and Jackson (1995) stated that even participants in the inferior arm of the trial get a psychological boost by continued monitoring and the rigour of the trial protocols. This was corroborated by one of the clinicians’ “even if there is no treatment (in the other arm of the trial) it involves a whole process of consent, explaining, somebody going to visit, having baselines done, screening done, follow ups. Those are the same. So, they have an opportunity of a professional, a clinician, a psychologist, a researcher spending an hour at times- doing assessments with them. That has therapeutic componence to it. So, I think for me and specially in the context of Pakistan, I feel that any kind of, even if it is treatment as usual, is better than having nothing at all”. (Khi – Int 08, Line 82 – 88 Dr O, female, 60 yrs, Psychiatrist). Based on this, it would be practicable to surmise that the clinicians will be satisfied to offer YCMAP as standard treatment of care. More research needs to happen in the cultural context of Pakistan to investigate how the clinicians’ collective belief model would impact
collective uncertainty of the expert community and thus disrupt clinical equipoise.

3. Some clinicians alluded one of the motivators for them for recruiting their patients in the RCT is that there may be no other treatment available to the patients otherwise. My case study was trialling a psychological intervention plus TAU vs TAU which may be regarded as low risk. In an RCT where the intervention would be pharmacological, the perception of risk being higher may have an influence on the clinician as to whether to recruit their patient in the RCT. This consequently may impact clinical equipoise. Further research on the concept of equipoise when using pharmacological therapies is required in Pakistan to gauge whether there would be an impact on clinical equipoise. Views of patients on how scientific methods fit within the cultural and religious practices are also needed.

4. There is a need to acknowledge the value of keeping the families engaged for support and ensuring compliance but at the same time to raise awareness, women/girls’ education and empowerment.

5. A positive drive for the clinicians to work with faith healers, religious leaders, policy, and law makers is required.

6. Some of the means of raising awareness and reducing stigma would be engaging community and religious leaders, schools and colleges and using social media and television as channels of health promotion.

7. Engaging policy makers by providing locally produced evidence base was important to put political pressure on policy makers both around decriminalising self-harm and suicide and improving mental health care services.
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Appendices

Appendix 1

Ms Rakhshi Memon

PhD candidate, University College London (UCL) UK and Pakistan Institute for Living & Learning (PILL)

Email: rakhshi.memon.18@ucl.ac.uk and phone no at PILL: 00921-35371084

Y-CMAP plus TAU or TAU alone: Which would you choose for your young patient at risk of self-harm?

Key:

Y-CMAP: Young people’s Culturally Adapted Manual Assisted Psychological Therapy (Talking Therapy)

TAU: Treatment As Usual (Standard routine care delivered by local, medical psychiatric and primary care services according to clinical judgement which could include anti-depressants)

This questionnaire is designed to find out whether or not you have preferences for either of the two treatments currently offered in the randomised controlled trial Y-CMAP. Participants in this trial are young people aged 12 to 18. On entering the trial, they are randomised to receive either Y-CMAP plus TAU or TAU alone. Y-CMAP is a new treatment that has been culturally adapted by Pakistan Institute of Living and Learning (PILL). We are interested in finding out what level of evidence you would want before prescribing this new psychological treatment routinely.

The project will form part of my PhD work through University College London (UCL), UK sponsored by PILL. All data obtained here will be collected and stored anonymously.

Anonymity

The survey is anonymous. We can’t link answers to you unless you give your name. If you do give your name or email, we will not pass this to any organisation outside our research team. All data will be collected and stored in accordance with the Data Protection Act 1998 in the UK.

Further information

If you have questions about the questionnaire, please email: rakhshi.memon.18@ucl.ac.uk

Before you start this study we need to check that we have your informed consent to participate. Once you have read the information sheet and consent form please tick the box below if you agree with the following statement.

- I understand the aim of this study and agree that its anonymised results are to be used for scientific purposes and further analyses.
First, we would like to ask you a few questions about yourself:

These first few questions in Part 1 are to find out some of your characteristics. It will help us compare your answers with those of other people who are similar to you.

**Gender:**
- Male [ ]
- Female [ ]

**Age:**
_____________________

**Faith:**
_____________________

**Ethnicity:**
_____________________

**Specialty:**
- GP [ ]
- Psychiatrist [ ]
- ED doctor [ ]
- Medical ward doctor [ ]
- Surgical ward doctor [ ]
- Other [ ]

**Years since graduation from medical school:**
_____________________

Yes – I agree [ ]
The next section explores your attitudes to choosing one treatment over another

For each question, please circle your chosen response category. We are measuring your attitudes so there is no right or wrong answer. Please do not spend too much time thinking about your responses to any single item. Usually, your first answer is your best response, so we advise selecting your first reaction to the item.

Response categories: 1=Mostly Agree, 2=Agree, 3= Disagree, 4= Mostly Disagree.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>1. Young patients at risk of self-harm who are receiving Y-CMAP plus TAU</td>
<td>1 2 3 4</td>
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<tr>
<td>plus TAU in the trial may not do as well as they would on TAU alone.</td>
<td></td>
</tr>
<tr>
<td>2. Young patients receiving Y-CMAP plus TAU may do better than they would</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>on TAU alone.</td>
<td></td>
</tr>
<tr>
<td>3. Treatment overall is better as a result of young patients’ participation</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>in the Y-CMAP trial.</td>
<td></td>
</tr>
<tr>
<td>4. There are other treatments outside this study which might be just as</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>good for them.</td>
<td></td>
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<tr>
<td>5. Y-CMAP plus TAU may not be any more effective than any TAU</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>6. I think that the Y-CMAP plus TAU is preferable to TAU alone for young</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>patients.</td>
<td></td>
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<tr>
<td>7. There is nothing on which to base a personal preference for Y-CMAP</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>plus TAU ahead of TAU alone for young patients.</td>
<td></td>
</tr>
<tr>
<td>8. Personal preference for YCMAP plus TAU is permissible despite collective</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>uncertainty amongst the scientific profession.</td>
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</tbody>
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If you have a preference, please answer the following question:

- I am confident in this preference.  
  | 1 2 3 4 |
- A personal preference could be based on factors independent of a clinical judgement of relative efficacy.  
  | 1 2 3 4 |

If you answered 4 or 5, please outline these factors

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

10. The randomised trial of Y-CMAP plus TAU and TAU alone is clinically needed despite any individual preferences for Y-CMAP plus TAU or for TAU alone.  
    | 1 2 3 4 |
11. The trial of Y-CMAP plus TAU and TAU alone should be sufficient to decide whether to offer YCMAP as a standard treatment for young people at risk of self-harm.  
    | 1 2 3 4 |
12. Please use this space to comment further on any of your above answers:
    ___________________________________________________________________
    ___________________________________________________________________
13. If you would like to participate in a face-to-face interview held at your workplace, please use this space to provide your contact details. Please note that these will not be appended to your responses above, and that when reporting the results of this survey you will not be identifiable from the responses.

14. If you would like to be sent a copy of the final report of this project, please use this space to provide your contact details. Please note that these will not be appended to your responses above, and that when reporting the results of this survey you will not be identifiable from the responses. The final report will also be available to download from the study website: www.ucl.ac.uk

Some final questions: (please respond only if you feel comfortable)

<table>
<thead>
<tr>
<th>Question</th>
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<tr>
<td>Do you know anyone amongst your friends or family who has died by suicide?</td>
<td></td>
</tr>
<tr>
<td>Do you know anyone amongst your friends or family who has attempted suicide?</td>
<td></td>
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</table>

Thank you for completing the survey.
Appendix 2: Information Sheet for Clinicians taking part in the Survey

Title: Ethics and randomised control trials in young people at risk of self-harm and suicide: the limits to equipoise and evidence

Background: Equipoise as a state of uncertainty is traditionally regarded as both the necessary and sufficient condition to justify randomisation of patients in clinical trials. However, there is little research on its potential role in justifying randomisation at multi-centre level.

Aims:

This project will examine:

1 the extent to which equipoise is a useful concept to justify randomisation at multi-centre level for evaluation of psychological interventions against Treatment As Usual including standard pharmacological interventions as in the Y CMAP programme;
2 what type and level of evidence is sufficient to persuade health professionals and policy makers to adopt psychological therapies in place of usual care so that they become first-line treatment instead?

Why have I been chosen to take part?

You have been chosen as you are a health professional concerned with the care of young people at risk of self-harm or suicide.

Do I have to take part?

No, you can decline to take part in the survey. It will not affect your professional practice in any way.

What will I have to do?

A short questionnaire will be sent to you, which you are asked to complete. It will take you roughly 10-15 minutes.

Would I be reimbursed for my time?

Regrettably, there is no funding for reimbursement of your time, but we have kept the questionnaire short and are grateful for your support

What are the benefits of taking part?

Little research has been done on this subject so you will be contributing to creating more knowledge and building the evidence base.

Will my taking part in the study be kept confidential?

Yes all information will remain confidential and stored as per Data Protection Act 1998 in the UK and PILL Data Protection Policy in Pakistan.

Further information and contact details:

I am a PhD candidate in research ethics at University College London (UCL) UK and I am conducting this survey as part of my thesis. I am grateful for your help in taking part in this study and if you require any further information please contact me on:

Email: rakhshi.memon.18@ucl.ac.uk  Mobile: +447710646262
Appendix 3

Topic Guide

Introduction
Thank you for seeing me today and offering to take part in this study. I would like first to outline the study so that you are able to decide whether you wish to proceed further.

Interviewer to:
- recap information sheet
- Explain process of recording, transcribing, analysing data from interview
- Outline process of data storage and protection
- Recap consent form
- Give time to interviewee to read and consider consent form
- If signing, need to sign consent form × 2 (one for participant with copy of information sheet, one for interviewer).

I have a list of topics that I hope to address over the next 40-60 minutes. Feel free to ask questions at any stage during the interview. I might make a few notes in case I want to come back to something later. If there is anything you do not feel comfortable discussing, then please do indicate and we can move on. If you would like to pause the tape at any point then please let me know, and we can either resume at a later stage or stop the interview.

1. What do you mean when you hear people talk about equipoise? (The Cochrane collaboration defines equipoise as “a state of uncertainty where a person believes it is equally likely that either of two treatment options is better” (www.cochrane.org).
2. What could be the reasons for using randomization for evaluation of psychological interventions against other treatments?
3. How comfortable are you with enrolling patients into RCTs that compare psychological intervention with no treatment? Would you feel more comfortable if the choice was between that treatment and some other treatment options?
4. What are your views about effectiveness of psychological treatments compared to drug treatment?
5. In your opinion is Y-CMAP plus TAU preferable to TAU alone for young patients?
   Prompt: If yes or no why is this so?
6. Have you got a sense as to what the outcome of the trial will be?
   Prompts: Do you think it will show that [psychological treatment] does make a difference.
7. What are the potential ethical issues that could arise while conducting the study?
8. What barriers should we consider while planning RCTs?
   Prompts: Cultural, moral and religious.

9. What could be the possible participant or his/her family’s reactions when asking
   to participate in RCTs?
   Prompts: Consent issue, privacy or confidentiality, some other concerns?

10. What are the needs, importance and scope of RCTs comparing psychological
    therapies with other treatment in our country?

11. What recommendations can you make for future efforts to evaluate
    psychological therapies for self-harm in Pakistan?

12. Is there anything more that you would like to add?

13. What is needed to persuade policy makers and funders, health professionals
    and participants to adopt psychological therapies instead of other treatments
    such that they become ‘standard of care’?
    Prompts: Increased awareness about research studies and evidence based
    practise, research as part of curriculums in colleges and medical universities.