Background paper:
Ethical issues arising in research with people with
mental health conditions

Meeting in Toronto, Canada, 8-9 June 2021 (tentative)

Purpose of this document

Meaningful research is required to advance the health of people with mental health conditions, but this has been stymied by a lack of mental health resources in low- and middle- income countries (LMICs) and the ethical and legal challenges faced by researchers globally. There is a need for a more nuanced understanding of how mental health is understood and experienced in diverse contexts, decisional capacity and how to assess it, how stigma and discrimination can be mitigated, and how to address the complex vulnerabilities that people living with mental health conditions may experience. These issues apply not only to mental health research but to research more broadly where exclusionary criteria may prevent the participation of people with mental health conditions resulting in an evidence base for their care that is poorer than for other populations. This is a significant issue given the comorbidity between mental health conditions and physical illness.
By addressing these ethical and legal challenges GFBR aims to advance the health of people with mental conditions by promoting their appropriate and ethical inclusion in research.

This document outlines the scope of the 2021 Global Forum on Bioethics in Research (GFBR) meeting theme and covers the following areas:
1. **Introduction**
2. **Maximising meaningful and impactful mental health research**
3. **Engagement and co-creation**
4. **Ethical challenges for the inclusion of people with mental health conditions in research**
5. **Governance**

Definitions and scope

The meeting will consider the ethical issues regarding the involvement of people with mental health problems in research. It will also focus on the ethics of mental health research. The exact content of the meeting will depend on the proposals that GFBR receives in response to the open call for applications (see below).

Mental health research encompasses a wide range of research fields including:
- Basic and clinical research (genetics, neuroimaging, psychology / clinical psychology, psychiatry/transcultural psychiatry, nursing, social care, primary care)
- Health systems research
- Social sciences (sociology, anthropology / cultural anthropology, bioethics)

Within this broad scope of fields, the range of potential studies can address prediction, prevention or treatment of mental health problems spanning from the testing of pharmacological treatments, to individual and group psychotherapeutic approaches, best-practice for in-patient care, and through to community-level preventative and mental health promotion approaches that may be integrated into other systems (e.g. education, or employment).

Many phrases are used to describe mental, neurological and substance use problems e.g. 'mental disorders', 'mental health conditions' and 'mental health problems'. When the GFBR Planning Committee discussed what terminology to use in this paper there was a desire to engage with a range of perspectives recognising the implicit biases the language we use can convey. As such, this paper uses the terms 'mental disorders', 'mental health conditions' and 'mental health problems'

interchangeably depending on the context. For example, when referring to biomedical initiatives the paper speaks of 'mental disorder' reflecting the language used in the World Health Organisation's (WHO) International Classification of Diseases; whereas in discussion of contested frameworks and conceptual understandings of mental health the phrases 'mental health problems' or 'mental health condition' are used as a way of being more inclusive and nuanced, reflecting perspectives that do not necessarily recognise or favour a biomedical explanation, or that regard the term 'disorder' as medicalised and stigmatising. The Planning Committee's discussion demonstrates the importance of language and how phrases may be favoured by some and contested by others. The Committee welcomes the submission of case studies that reflect on the ethical challenges raised by language in mental health research.

It is recognised that mental health conditions are a heterogeneous range of problems that originate due to a complex array of biopsychosocial factors (i.e. genetic, biological, psychological, environmental and social)[i]. In addition, their effects on individuals vary greatly in terms of severity and decisional capacity, which for many people will not be impaired. Despite their differences, these problems are grouped for the purpose of this paper because they share a number of ethical issues regarding the inclusion of people with these conditions in research, including the potential for:
- competing epistemological mental health explanatory frameworks (i.e. competing understanding and framing of a mental health "problem" - which may arise between researchers who ascribe to different positivist / interpretivist epistemologies; as well as between researchers and participants due to cultural differences. The competing understandings – similar to those found for physical disorders – have ethical implications for who is included / excluded in how research is framed (e.g. linking to community participation or co-design approaches) and funded (e.g. who sets the priorities and how do these influence global flows of knowledge and power?);
- varying degrees of decisional capacity;
- stigma, discrimination and abuse;
- vulnerability and involuntary commitment (e.g. due to dependency on family members or medical services or due to symptoms associated with the mental condition);
- exclusion, in particular from non-mental health research.

The upcoming GFBR meeting will provide an opportunity for stakeholders (e.g. bioethicists, researchers, scientists, funders, policy-makers, experts by experience) to engage in rigorous critical assessment of these ethical issues through discussion of real-life LMIC case studies. While the exact content of the meeting will depend on the proposals we receive, potential topics include conceptualisations of mental health problems and how to maximise impactful research through research prioritisation and methodology, including consideration of inclusion and exclusion criteria. The meeting will also be an opportunity for rich, cross-country comparison of the range ethical issues listed above.

The meeting does not intend to focus on the general ethical issues regarding research approaches e.g. genomics and biobanking. However, case studies situated in these research approaches are encouraged if the ethical issues are specific to the inclusion/exclusion of people with mental health conditions. For example, a genomics project that has investigated ethnopsychological[1] understandings of mental ill-health to inform consent procedures and help devise plans to reduce stigma would be a strong case study in comparison to a genomics project that focuses solely on the need for fair international collaborations.

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[1] This captures the systems of the self, emotions, human nature, motivations, personality and the interpretation of experience by a specific cultural group.

This paper is being published with the call for case studies and proposals on governance issues. The GFBR organisers are looking for interesting and important cases that are relevant to the theme. The organisers are not being prescriptive and so the actual topics considered at the meeting will be defined by the case studies and governance papers that are submitted. In this way, GFBR aims to be responsive to applicants and the issues that they consider most important.

We indicate below some examples of issues considered important by the organisers, but these are not exhaustive and are intended only as examples. Case studies should focus on research in LMICs and could address (but are not limited to) one or more of the following questions:

Conceptualisation of mental health problems
- Do current approaches to mental health research resonate with how mental health problems are conceptualised by varying stakeholders in LMICs?
- What are the ethics of choosing different conceptual frameworks? Is it best to go with current clinical frameworks or to go with local conceptualizations and what if either of these have important scientific flaws?
- How can the methods applied to measure mental health symptomology best reflect local conceptualisations of mental ill-health/wellness?
- To what extent do conceptualisation of mental health problems lead to the systematic exclusion of those experiencing such problems from research?

Maximising impactful, locally-relevant research
- How can meaningful, impactful and ethical mental health research be maximised (e.g. through research prioritisation – how should this be undertaken and who should be involved; by adopting context-appropriate and feasible methodologies, and ensuring the feasibility of implementing research outcomes within the resources available to mental health systems in LMICs)?
- What values and world views should guide the development and prioritisation of mental health research (e.g. solidarity, respect, autonomy or inclusiveness and epistemic values of tractability, explanatory potential etc.)?
- How can relevant values and belief systems in specific settings be identified and incorporated to ensure research is most relevant to LMICs?

Engagement and co-creation
- What methods can be used to engage people with lived experience of mental health conditions to promote inclusion and co-creation of mental health research methods and practice?
- Who else should be engaged during research design and implementation (e.g. carers, local communities etc.), how and for what purpose (e.g. for setting priority topics to explore, to inform the design and conduct of the research, as part of an anti-stigma campaign etc.)?

Inclusion/exclusion
- What ethical values are balanced in determining the inclusion / exclusion of people with mental health problems in research (e.g. equity, protection from harm, etc.)?
- How do research eligibility criteria impact on the participation of people with mental health problems in research?
- How can over exclusion be addressed and the ethical inclusion of people with mental health problems be promoted?

Stigma leading to discrimination and abuse
- What is the ethical duty of researchers to assess and address mental health stigma as part of their research?
- What approaches can be used to aid cultural understandings of stigma towards those with mental health problems (e.g. research methods, co-design approaches etc.)?
- What strategies can researchers adopt throughout the research process to mitigate or address mental health related stigma (including how research is conducted and specific interventions to reduce stigma)?

Capacity
- How can researchers provide for people where capacity is lacking, absent, in question or fluctuates, and what is the moral duty of researchers in this process (e.g. to assist them in being able to consent and to protect those who can't)?
- Is there a way to have a more meaningful understanding of capacity in relation to mental health status?
- How do researchers in different countries define and assess capacity to consent to research and what ethical, governance or legal issues have they encountered in making these assessments?

Governance
- Are current ethics governance structures, processes and practices fit for purpose to support the inclusion of people with mental health conditions in research?
- What regulatory models do different countries use to include people who lack capacity to consent (e.g. who decides on behalf of the individual; is a lasting power of attorney or an advance directive possible or applicable to research consent; are the courts involved in appointing a surrogate decision-maker; is this decision-maker legally recognised or recognised 'in practice' (e.g. a family member); does the model promote inclusion or increase the likelihood of exclusion?)
- Does a country's governance structure and regulation support or challenge the ability to conduct research with people who have mental health conditions and lack capacity (e.g. in relation to how capacity is defined and the provisions (if any) for surrogate decision-making)?

1. Introduction

The need for research to advance good mental health

The WHO estimates that untreated mental health disorders account for 13 percent of the total global burden of disease, and that by 2030, depression alone will be the leading cause of disability around the world.[ii,iii] By the same year it is estimated that 75 million people worldwide will be living with dementia, rising to 131.5 million by 2050.[iv,v] Eighty percent of the people likely to experience mental health problems in their lifetime come from LMICs[vi] yet the treatment gap - the percentage of individuals who require treatment but do not receive it due to a variety of reasons - is more than 75% in many LMICs.[vii] The corresponding range in high-income countries (HIC) is between 35% and 50%, highlighting that the treatment gap is a global concern.

It has been argued that the term 'treatment gap' carries a medical connotation and implies biomedical treatment (or lack of it) for mental health problems[viii], excluding psychological and social care approaches that can be more valuable and effective than medical treatment in the case of many mental health issues. Because the term treatment gap signifies biomedical treatment, policy makers prioritise improvements to medical services and put less emphasis on psychological and

social care pathways leading to a 'care gap' for mental health problems, reflecting broader debates about the social model of disability.

Over the last ten years, good mental health has been recognised as a global priority:

- The UN Convention on Rights of Persons with Disabilities was adopted in 2006 and includes provisions on capacity, decision making and promoting research. The Convention introduces a paradigm shift from the 'medical' to the 'social' model of disability and reaffirms that all persons with all types of disabilities must enjoy all human rights and freedoms, such as dignity and individual autonomy.[ix]

- In 2011 the Grand Challenges in Global Mental Health initiative stressed the need for all care and treatment interventions — psychosocial or pharmacological — to have an evidence base to provide programme planners, clinicians and policy-makers with effective care packages.[x]

- The World Health Assembly Mental Health Action Plan 2013–2020 represented a formal recognition of the importance of mental health for the 194 member states of the WHO. It is a commitment by all member states to take specified actions to improve mental health and contribute to a set of agreed global targets, which included the need to strengthen information systems, evidence and research for mental health.[xi] The Plan has been translated into regional action plans – for example in the Eastern Mediterranean Region[xii] – demonstrating its relevance to LMIC settings.

- The global importance of good mental health is also reflected by its inclusion in the Sustainable Development Goals in 2015.[xiii] For example, SDG targets 3.4 states that 'By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being.[xiv]

- In 2016 the World Bank recognised the burden of mental health problems on society, accounting for almost one in three years lived with disability globally. It called for mental health to become a global development priority, recognising the economic burden of mental health disorders in terms of both decreased productivity due to disability and the co-morbidity of mental disorders with other diseases (e.g. cancer, HIV, cardiovascular disease) that impact negatively on health and welfare systems. The need for new sources of funding from national governments and international development partners was recognised as being required to bridge resource gaps and provide cost-effective mental health interventions.[xv]

- The Lancet Commissions on global mental health (2007 and 2018) assessed the state of the field and made recommendations. Importantly, the 2018 Lancet Commission builds on the original piece by further emphasising the importance and role of the cultural context on shaping experiences of and responses to mental health problems.[xvi]

While there has been an escalation of mental health research in the last 10 years it has been compromised by ethical challenges (e.g. relating to stigma, risk, vulnerability and capacity to consent). In addition, the bulk of current research has taken place in HIC where only a small proportion of the world's population live. As such, little of the published mental health research is directly pertinent to infrastructural and societal contexts of individual LMICs, precluding the development of mental health policies based on robust evidence and local priorities.[xvii] Notwithstanding that there are universal aspects of mental disorders and their treatments, there is a need for contextual LMIC research that is driven by the disease burden and priorities in those countries, and that takes account of the local values, preferences, and feasibility issues.[xviii] This need is challenged in some LMICs, however, by the lack of professionals (e.g. psychiatrists, clinical psychologists, psychiatric nurses, psychiatric social workers and mental health researchers) and other mental health resources, the low prioritisation of mental health by governments, the low policy priority for mental health[xix] and the lack of human rights-oriented and community mental health approaches.

Conceptualisation of mental health problems

Do current approaches to mental health research resonate with how mental illness is conceptualised by varying stakeholders in LMICs?

What are the ethics of choosing different conceptual frameworks? Is it best to go with current clinical frameworks or to go with local conceptualizations and what if either of these have important scientific flaws?

How can the methods applied to measure mental health symptomology best reflect local conceptualisations of mental ill-health/wellness?

To what extent do conceptualisation of mental health problems lead to the systematic exclusion of those experiencing such problems from research?

Conceptualisations of, and responses to, mental health problems are strongly influenced by factors such as early life experiences and socio-cultural context.[xx] While there are standard methods for diagnosis and categorisation of mental health problems, these have mostly been developed in Western contexts. Such methods bring challenges in cross-cultural and multi-lingual contexts[xxi] where they may not be consistent with individuals' belief systems, or participants may reject diagnostic labels.[xxii,xxiii] This may particularly be the case where people fear stigmatisation and discrimination or where local, culturally informed judgements about what is normal and abnormal conflict with global criteria for diagnostic categories of mental ill-health. Diagnosis has also been criticised for its dehumanizing and "objectifying" effects that, multiplied by stigmatising societal attitudes, engender self-stigma.[xxiv] However, some people may experience advantages related to a diagnosis including reassurance that their situation is not unique, providing a platform from which to communicate about their experience, and as a critical foundation for accessing resources and intervention options.[xxv]

Different world views or epistemologies that exist across the world may inform attitudes to mental health problems and these will likely be specific to individual countries and regions that have shared social and cultural norms. A recent social science project investigated if, and how, attitudes towards psychosis in Ghana relate to the three main theoretical frameworks of reference shared by many Ghanaians: Western secularized value systems; traditional beliefs; and religious (Christian and Muslim) conceptions of human life.[xxvi] Responding to a vignette and image of someone experiencing psychosis people used variations of "mentally ill/problem", followed jointly by "abnormal" and "mad/mad man" to describe what they saw. In addition, common phrases include "he has something wrong in the mind". The authors highlight the importance of a linguistic clarification of the conception of mental health and that the use of the word 'mental' itself requires unpacking since the local languages do not always make a clear distinction between the 'head' and the mind.[xxvii,xxviii,xxix]

People with mental health conditions may have mixed beliefs about their illness e.g. perceiving it as neurological and/ or psychiatric and/or socially-determined[xxx], and also conceiving it as spiritual or mystical. Research by Matshabane found that much of the mental illness literature from Africa - documenting the perspectives of the general public, traditional healers, health care practitioners, patient carers and patients - suggests that individuals from a variety of African cultural groups primarily attribute their disease to cultural or supernatural causes, and that this is similar to the findings by scholars in other LMICs, such as India and Malaysia,[xxxi, xxxii] and in HICs.

In this context, people from LMICs – and HICs – may access both Western and traditional treatments (e.g. herbal medicine, religious healing) and consultation with traditional healers. The study of Ghanaian attitudes to psychosis found that although biomedical treatments (i.e. psychiatry and psychology) were reported by respondents as the most important for psychosis, there is not a singular treatment preference for psychosis, as most people showed a clear preference for multiple healthcare streams[xxxiii], as would likely be the case in other LMICs and HICs. Various interpretations might be drawn from this, including that the perception of health is more focused on elimination of the condition than of managing it. As a result, biomedical cures that offer solutions which require continuous medication are perceived as not 'curing' the condition. So, people may recur to other solutions that promise total 'cures' in addition to seeking biomedical healthcare. Linked to this is also the challenge of affordability, access and sustainability of obtaining drugs over a lifetime or a prolonged period. [xxxiv]

Conceptualisations of mental health problems will have implications for research consent and community engagement and will require researchers to develop methodologies that are sensitive to these beliefs. To this end, it is important for researchers to gain an understanding of causal beliefs, many of which may vary across different mental health conditions, contexts and cultures.[xxxv]

Mental health classification systems – what they mean for research

There are two key classification systems for mental health disorders:
- *The Diagnostic and Statistical Manual of Mental Disorders* (DSM) defines and classifies mental disorders in order to improve diagnoses, treatment, and research. Developed by the American Psychiatric Association, the manual was first published in 1952. Since then the manual has been further developed with the goal of providing precise definitions of mental health disorders for clinicians and researchers by providing diagnostic criteria sets and descriptive text. The fifth and current edition (DSM5) was published in 2013.[xxxvi] This version explicitly recognises that "all forms of distress are locally shaped, including the DMS disorders"[xxxvii] and includes a cultural formulation interview intended to elicit information about the sociocultural context in which difficulties are experienced. This demonstrates the influence of those critical of the lack of cultural sensitivity of universalised diagnostic criteria.
- The WHO's *International Classification of Diseases* (ICD) is a diagnostic classification standard for clinical and research purposes and includes a section on mental, behavioural or neurodevelopment disorders.[xxxviii] The primary function of the ICD is to facilitate the reporting and monitoring of standardised, basic health statistics.[xxxix]

The DSMs and ICDs share broad features in providing a categorical scheme of mental disorders. The disorders are identified on the basis of descriptive explanations, using polythetic criteria to be combined with clinical observation of the number and type of an individual's symptoms and their self-report.[xl] This emphasis recognises that causes for mental disorders are multiple and intersecting, so that an etiological classification will never be possible in this area. DSM5 was developed to facilitate, and promote the validity and reliability of diagnosis in a clinical setting, and is also used in research contexts. Some have argued that classification systems have in many ways given impetus to mental health research, while others have highlighted the potential negative implications of symptom-based diagnosis on research.[xli]

The approach to diagnosis classification inherent to the DSM and ICD have been the subject of historical and ongoing critique, notably in the field of transcultural psychiatry – a diverse movement which integrates anthropological interest in cultural influences on mental health and societal responses, and the experiences of Global South psychiatrists trained in the Global North and attempting to apply universal diagnosis to local populations.[xlii] This field, and the work of countless

anthropologists, sociologists, experts by experience, and biomedical researchers, have identified the marginalisation of alternative ways of knowing, being and thinking in the epistemic frameworks embedded in and promoted through systems of classification.[xliii] These concerns echo broad debates about the utility and validity of psychiatric diagnoses, including problems of diagnostic heterogeneity[xliv] and that systems of classification risk pathologising multiple aspects of our lives - such as grief, or childhood inattention – leading to the potential for diagnosing and treating "mental illness" in what is a normal reaction to adverse events.[xlv]

In a global context these debates have been complemented by the field of *ethnopsychology*[xlvi] including notably work into *idioms of distress* which examines the role of language and culture in how distress and wellbeing is understood, experienced, and communicated.[xlvii] Such perspectives question the universality of psychiatric categories to foreground that idioms of distress can communicate suffering that does not reference psychopathological states and may for example express collective social anxieties.[xlviii] Problems relating to the cross-cultural relevance of mental health classification systems are carried over into the measurement of distress and wellbeing via standardised symptom scales commonly applied in mental health research.[xlix] It is important to note however that there are likely universal features to mental ill-health, such as have been described in relation to depression.[l] Furthermore, it has been shown to be possible to adopt a balanced approach that acknowledges universal features of mental disorders, alongside the contribution of contextual and cultural influences.[li]

2. Maximising meaningful and impactful mental health research

How can meaningful, impactful and ethical mental health research be maximised (e.g. through research prioritisation – how should this be undertaken and who should be involved; by adopting context-appropriate and feasible methodologies and ensuring the feasibility of implementing research outcomes within the resources available to mental health systems in LMICs)?

Research priorities

What values and world views should guide the development and prioritisation of mental health research (e.g. solidarity, respect, autonomy or inclusiveness and epistemic values of tractability, explanatory potential etc.)?

How can relevant values and belief systems in specific settings be identified and incorporated to ensure research is most relevant to LMICs?

Important global issues for mental health research priority setting include:
- how to ensure sufficient attention to mental health at each stage of the life course (e.g. recognising that the majority of mental health problems onset before 15 years of age, and that there are other mental health problems specific to life-stages such as maternal mental health and late-onset conditions including dementia)
- how to balance basic, discovery research (e.g. into the physiology of mental illness) versus research into mental health interventions, promotion and care (including addressing the social determinants of mental ill health)[lii,liii]
- which outcome measures should be prioritised (e.g. food insecurity)
- how to set research priorities when populations have differing access to treatments (e.g. access to a particular drug may be restricted in low resource settings, or if a type of talk therapy will be hard to reproduce in contexts where there are few qualified mental health professionals)
- at what level research priority-setting should take place (country, regional or global)

- how to set up fair processes for research priority setting (e.g. who should be included, what principles and values should be used, and the coordination of funders, etc.)
- challenges for the engagement of policy makers (e.g. low perceived legitimacy of the problem of researching and implementing mental health services and inadequate government support)[liv]
- the role of funders and their impact on priority setting
- the dominance of research funding by the pharmaceutical sector, with psychosocial research less well funded, leading to a selective focus of an evidence base towards biomedical aspects of etiology and treatment. Some have highlighted the potential harm caused by psychiatric drugs and the conflict of interest between pharmaceutical companies and academic medicine.[lv] Others have emphasized that the industry has brought significant gains to mental health across the globe, for example, through the availability of generics for common mental disorders.

Mental health research capacity and infrastructure in many LMICs are limited, with little dedicated funding, a scarcity of trained mental health research personnel and a dearth of infrastructural support.[lvi] These limitations call for context-specific research prioritisation and methodologies to maximise scare resources to produce meaningful and impactful outcomes (i.e. preventions or treatments that can feasibly be implemented). A very successful example of this is the Friendship Bench in Zimbabwe where lay health workers are trained to deliver evidence-based problem-solving therapy. The project focuses on people who are suffering from common mental health problems, such as anxiety and depression, known locally as kufungisisa; translated to 'thinking too much'.[lvii] It has trained 600 elderly women, reached over 70 communities, both rural and urban in Zimbabwe, and has been adopted in other LMICS and HICs.[lviii]

The link between physical health and mental health has increasingly been recognised, along with the need to integrate mental health research and therapies into existing care platforms to maximise resources, reduce stigma, and promote a holistic view of health as encompassing physical and mental health. Research in Uganda found that a group support psychotherapy intervention delivered by lay health workers, among people living with HIV in rural areas, resulted in a reduction in depression and better HIV treatment outcomes. The programme attracted both men and women and this was attributed to the intervention being developed in consultation with community members with depression and it being tailoring to the social context.[lix] The authors concluded that given the normally low participation of men in health interventions in low- resource settings, integration of the intervention into existing HIV care platforms might confer additional value by engaging men in HIV treatment services, thereby improving the health of the entire community.

Another example of integration of mental health services into other systems is the School Health Implementation Network: Eastern Mediterranean Region. The network spans Egypt, Pakistan, Iran and Jordan and focuses on mental health promotion, prevention, and early intervention with school-aged children. It applies a task-sharing intervention with teachers and other school staff including school nurses, counsellors and psychologists, with links from the education to mental health systems to ensure appropriate tiered interventions to meet the range of child mental health needs present in schools.[lx]

Research methodology

The key challenges in relation to mental health research methodology include:

Measurement of mental health: *How valid are mental health constructs and instruments measuring these constructs in diverse socio-cultural-linguistic settings?*

As highlighted above, there are recognised problems with mental health classification systems such as the DSM and ICD, notably including their relevance to diverse socio-cultural settings. These problems are carried over into the measurement of distress and wellbeing via standardised symptom scales that are commonly applied in mental health research. These issues strike at the heart of the validity of global mental health research.[lxi]

Efforts have been made to develop methods for the translation and cultural adaptation, or local development, of mental health measurement tools in an effort to ensure their validity in diverse local settings.[lxii, lxiii] Importantly, this research has demonstrated variability in the experience and manifestation of mental distress, leading to questions about the extent to which instruments founded upon a Western biomedical framing of mental illness can be brought to bear on the detection of mental illness and measurement of mental health outcomes across languages and cultures.[lxiv] There are furthermore challenges to the administration of such measurement tools in settings with high rates of illiteracy or without a writing system. These issues raise important questions about the ecological validity of such measures in diverse settings, and challenge the validity and reliability of mental health research.

Standards of care: There are contexts where the local standard of mental health care is below the standard offered by the research project and may be bad enough that it would be regarded as malpractice by many practitioners (e.g. physical restraint by chaining[lxv,lxvi]). This raises a question of what standard of care is appropriate and culturally acceptable in research conducted in such contexts? And who is responsible for funding the baseline standard of care (national health systems, or research projects themselves)? In addition, researchers can be faced with the challenge of balancing care for research participants with the need for data that is relevant to the population being studied. Improving the local standard of care too much may result in research data that does not give information that is relevant to local decision-making about what to provide through the public health system.[lxvii]

Control arms and the use of placebos (see Section on Risk).

Digital tools and phenotyping: *What ethical framework can be developed to create robust and relevant digital innovations in mental health research for LMICs?*

Use of digital tools (e.g. using mobile devices and social media) have potential for capturing mental health-related data directly from individuals and delivering individualised self-help in a cost-effect way.[lxviii] The tools could be useful in a range of research and treatment scenarios but may be especially effective as part of an early intervention approach. Emerging evidence suggests that the large majority (75%) of mental health problems have their onset between 15 and 24 years of age. Given the prevalence of smartphone ownership in this age group in both HIC (90%) and LMICs (50%), digital tools could have an important role to play in the early detection and intervention for mental health in this group.[lxix]

Digital phenotyping involves the collection of large amounts of physiological and biometric data gathered by smartphone and other personal digital devices to provide continuous, passive assessment of behaviour, mood, and cognition by applying machine learning.[lxx] It has primarily been used to measure mental health and is currently being validated in large scale trials.[lxxi]

Emerging uses of digital technology in mental health research raise issues around privacy, informational autonomy and acceptability that require consideration by regulatory bodies, governments and funders. Digital technologies also raise issues of equity when people who do not

have access to smartphones get excluded. Research ethics committees (RECs) have an important role in assessing study design and providing an additional layer of safeguards for emerging digital approaches that collect large-scale data. However, digital phenotyping may pose challenges for RECs, as they may not be aware of potential risks and full ramifications of the data collection.[lxxii]

3. Engagement and co-creation

What methods can be used to engage people with lived experience of mental health conditions, to promote the co-creation of mental health research methods and practice?

Who else should be engaged during research design and implementation (e.g. carers, local communities etc.), how and for what purpose (e.g. for setting priority topics to explore, to inform the design and conduct of the research, as part of an anti-stigma campaign etc.)?

Increasingly researchers are recognising the need to include people with lived experience of mental health conditions ('experts by experience') in decisions on what is researched and throughout the design, conduct and implementation of research.[lxxiii, lxxiv] Experts by experience can also be involved in disseminating information and knowledge about research and its findings and play an active role in lobbying policy makers.[lxxv] Such inclusion is founded on ethical values such as equal respect for persons; fairness; accountability and human rights principles of the right of people with lived experience to be heard in decisions affecting them.

Engagement seeks to empower experts by experience by recognising and responding to their expression and experience of mental health. In addition, it can help researchers adopt context sensitive methodologies that are feasible and acceptable to individuals.[lxxvi] Involvement of experts by experience may be especially important for developing research protocols and consent processes for research that intends to recruit people who lack capacity to consent.[lxxvii]

In Ethiopia, experts by experience have been integral to research on how to achieve involvement of experts by experience in mental health system strengthening.[lxxviii] A Theory of Change model was produced with a range of stakeholders, including experts by experience and caregivers. A Participatory Action Research approach was then applied and stakeholders - including experts by experience - identified top local priorities that need to be addressed to achieve involvement. A smaller Research Participant Group (RPG) comprising experts by experience, caregivers and health professionals was then established and worked together to explore in more depth the priorities identified by the stakeholders. An action plan was then developed, which the RPG is implementing with assistance from academic researchers.

Representation of experts by experience is being championed by national and global organisations. The Global Mental Health Peer Network aims to give voice to the views, opinions, perceptions and experience of people with lived experience of mental ill-health at both local and international levels.[lxxix] There are some examples of national organisations that advocate for involvement in research specifically, potentially in response to the statutory context of that country which introduces a duty to involve.[lxxx] However, to the GFBR Planning Committee's knowledge this element of advocacy is not widely practised in LMICs and advocacy organisation generally have a broader remit (e.g. including running campaigns and involvement in service delivery development). It may be interesting to discuss at GFBR whether networks that advocate for inclusion in research should be established in LMICs, with links to the national or regional policy context.

While involvement may bring personal benefits for experts by experience (e.g. greater self-awareness, self-respect, self-esteem, and self-confidence and improved quality of life), exposure to parts of mental health and research systems may lead to shifting perspectives with unintended negative outcomes (e.g. disillusionment and potential disengagement from services). Patterson et al call for experts by experience to be informed about the potential benefits and risks of involvement, and for further research to explore the impact of involvement on individuals.[lxxxi]

Tokenistic involvement is also problematic, whereby pre-existing power differentials exacerbated by stigma lead to the views of experts by experience being over-ridden or dismissed, even if they are present at the table. Methods to enable full involvement need to be developed and tested, with Participatory Action Research as one promising approach[lxxxii], and use of photovoice methodologies another[lxxxiii].

A systematic review of the ethical challenges in the mental health care context identified that there is a perception that 'autonomy' in some communities does not just pertain to the individual but rather the individual-caregiver dyad.[lxxxiv] This raises a question about whether caregivers - who bring their own experience and perspective - should be given special status alongside experts by experience, and how and for what reason carers should be engaged in research. Specific guidance for involving carers in mental health research is absent in many countries, with some notable exceptions[lxxxv]. Qualitative research in Australia, involving carers and experts by experience, identified potential concerns regarding carer participation in research, including story ownership. Communication between researchers and carer-participants and within the individual-caregiver dyad was considered key to minimise potential risks to privacy and of social harm to the carer-participants' relationships.[lxxxvi]

Several barriers to participation of experts by experience have been identified including stigma within the health system, the local community and individuals, the lack of a specific strategy or model to guide how best to involve experts by experience and caregivers, and a lack of clarity about the roles and responsibilities of the different parties. [lxxxvii] Financial and other resource constraints may be a barrier for some researchers in adopting a robust process for engagement.

4. Ethical challenges for the inclusion of people with mental health conditions in research

Many practical ethical issues are likely to arise in the context of the care and treatment of research with people with mental health problems. Some of these will not be knowable in advance because they'll depend on the specifics of the situation. Others might be knowable and are standard concerns in research ethics e.g. issues relating to privacy and confidentiality. These issues will not be addressed in any detail here, instead this section focuses on the key challenges specific to research involving people with mental health problems.

Inclusion/exclusion
What ethical values are balanced in determining the inclusion / exclusion of people with mental health problems in research (e.g. equity, protection from harm, etc.)?

How do research eligibility criteria impact on the participation of people with mental problems in research?

How can over exclusion be addressed and the ethical inclusion of people with mental health problems be promoted?

The Council for International Organisations of Medical Sciences (CIOMS) international guidelines state that adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion.[lxxxviii] This recognises that the central ethical and human rights consideration for adults who lack decision-making ability is inclusion.[lxxxix] In addition, it recognises that the value and impact of research may be detrimentally affected by exclusionary criteria, if the selected participants are not representative of the real-world population to which a study is intended to apply.[xc] Exclusion of individuals who have reduced or no capacity, and who may have several mental or physical co-morbidities, reduces the generalisability of the research results and consequently, the evidence base for their care is poorer than for other populations.[xci] Over exclusion can be an issue in all health-related research (i.e. mental health research, physical health research, or research exploring social determinants of health).

Humphreys et al examined the prevalence of reported psychiatric exclusion criteria using a sample of 400 highly-cited randomized trials across 20 common chronic conditions (6 psychiatric and 14 other medical conditions). Psychiatric exclusion criteria were found to be employed in at least half of the clinical trials with psychiatric treatment trials being the most likely to report psychiatric exclusions. Recognising that published clinical trial reports do not always fully describe exclusion criteria, Humphreys et al considered that their study's estimates of the prevalence of psychiatric exclusion criteria are likely conservative and that as a matter of clinical and social justice more attention should be paid to how individuals with psychiatric problems can be safely included in medical research.[xcii] Blanket assumptions about an individual's capacity to consent were considered a likely reason for exclusion, even though research has shown considerable within-group heterogeneity.[xciii] An additional reasons for exclusion may be stigma from the researchers.

People living with a mental health condition may be invited to take part in non-mental health research studies and have the capacity to consent to participation. Often, such studies do not ask about mental health conditions during the recruitment process and so researchers do not have the opportunity to consider what support an individual may need to successfully participate in research. Not providing this support could undermine the individual's health or the legitimacy of the study (e.g. if there is a lack of adherence to a treatment plan). This is not to suggest that people with mental health conditions should be privileged; there are a range of conditions and considerations that affect a person's participation that mean they would benefit from additional support (e.g. low literacy). However, if researchers are aware of the individual's mental health condition from the off-set this gives them the opportunity to support their participation and inclusion in research.

Decisional capacity

How best can researchers provide for people where capacity is lacking, absent, in question or fluctuates and what's the moral duty of researchers (e.g. to assist them to be able to consent and to protect those who can't)?

Is there a way to have a more meaningful understanding of capacity in relation to mental health status?

How do researchers in different countries define and assess capacity to consent to research and what ethical, governance or legal issues have they encountered in making these assessments?

Capacity relates to a person's unique characteristics and to their ability to make a particular decision at a specific time and in a specific situation[2]. Decisional capacity is widely viewed to be comprised of four elements:

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[2] The term 'competency' is also used in the literature but this paper will use the term 'capacity'.

- *Understanding* of the facts involved in the decision
- *Appreciation* of the nature and significance of the decision that they are faced with
- *Reasoning* and the ability to manipulate information rationally (e.g. weigh risks and benefits)
- *Choice* i.e. the ability to express a preference.[xciv]

If a person is considered to have diminished or no capacity, researchers would ideally be required to conduct a capacity assessment. However, laws, research policies and study protocols are often silent about when and how capacity should be assessed.[xcv] Researchers have a formidable conceptual and normative task of determining what capacity is, how it should be defined, and the epistemic question of how they can know an individual meets certain standards for capacity.[xcvi] Research has shown that different mental health conditions and different research contexts (e.g. following an emergency) may disrupt different aspects of capacity, with implications for consent procedures.

As mentioned above, assumptions about capacity across and within types of mental health conditions may lead to exclusion despite evidence to suggest in-group heterogeneity. This not only reduces the generalisability of the research findings but denies people with mental health problems the opportunity to express their altruism and autonomy through research participation.[xcvii] Research by Roberts et al assessed the views of clinically diagnosed patients with schizophrenia, finding they strongly supported schizophrenia research and autonomous decision making by participants and saw helping others and helping science as important reasons for protocol participation.[xcviii] For both scientific reasons and for the principle of justice, a more nuanced understanding of capacity is required to promote the inclusion of people with mental health problems in research.

CIOMS, along with other guidelines, contain provisions for research involving persons with impaired decisional capacity (see Box 1) and stipulate or recommend special procedures. For example, the guidelines identify the need for adequate and potentially repeated capacity assessments and permission of a legally authorised representative (LAR) of the person who is incapable of giving informed consent, taking account of their previously formed preferences, values and beliefs (if any) (see Section 5 for more on LARs). However, current guidelines do not elaborate on how the multidimensional nature of capacity should be understood, assessed and managed.

The challenges of assessing capacity can be especially complex given that an individual's capacity may vary over time and fluctuate or diminish during the course of a research study, raising uncertainty over the ongoing validity of consent.[xcix] This reinforces the need for capacity to be assessed independently of the illness and for assessments to be repeated if capacity is likely to fluctuate (e.g. during medium- and long-term studies).

A previous GFBR meeting on this topic identified the need for awareness of the possibility of conflict of interest if researchers are themselves involved in the determination of capacity for research.[c]

> **Box 1.** The CIOMS international ethical guidelines for health-related research involving humans make a number of provisions relating to an individual's capacity to consent:
> - competence or decisional capacity is determined by the ability to understand material information, appreciate the situation and its consequences, consider the treatment options, and communicate a choice.
> - persons should be considered capable of giving informed consent unless it is proven otherwise.
> - a lack of decisional capacity is time-, task- and context-specific.
> - when researchers have reason to believe that potential or current participants are incapacitated, the participant's decisional capacity must be adequately assessed. In cases where incapacity to give informed consent might reasonably be expected, participants must be routinely screened.
> - diagnosis of a mental or behavioural disorder does not necessarily imply that individuals are incapable of giving informed consent.

Historically, guidelines have categorised individuals who lack capacity as a 'vulnerable' group. However, in recent years discussions in the bioethics literature have moved away from labelling entire groups as vulnerable.[ci,cii] Definitions of vulnerability have been critiqued for their potential to stereotype and stigmatise participants and to promote paternalistic behaviours in researchers.[ciii] Rather than presuming vulnerability, research with individuals who lack capacity should be evaluated from the lens of special scrutiny. That is, to subject research with individual's who lack capacity to more thorough ethics review, and to consider how to strengthen or provide more targeted forms of protection to safeguard the participants' rights and welfare depending on their circumstances (e.g. their level of decisional capacity) and the nature of the specific decision (e.g. the complexity of the research design). This may involve having:

- consent materials tailored to different levels of capacity
- having multiple encounters to explain the study
- checking participant comprehension with open-ended questions and providing corrective feedback (understanding that to comprehend what a researcher wants to do does not mean to understand it the way the researcher does)
- allowing extra time for the potential participant to decide whether or not they would like to be involved, and
- allowing time for them to discuss the research with others (family, support workers etc.).

It is key for researchers to recognise when a capacity assessment appears needed, to have tools available to provide a capacity assessment when indicated, and to have protocols in place to act on the findings.[civ]

Tools to assess capacity

Tools to assess capacity have been developed, including the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC).[cv] This provides a short, efficient means of screening for potential decisional incapacity and can be conducted by a researcher with basic training.[cvi] The tool offers an alternative as a first line approach before considering a more comprehensive assessments, such as The MacArthur Competence Assessment Tool-Treatment (MacCAT-T).[cvii] Evidence for use of these tools has been generated in HICs, with a lack of evidence in LMICs, with some exceptions[cviii] which suggest that these approaches show promise for LMIC research.

Charland[cix] provides an account of research by Tan et al[cx] that involved a MacCAT-T assessment and collection of additional qualitative data from anorexic patients who wished to refuse treatment. Charland argued that there is a foundational problem with the theory of the MacCAT-T and other tests for decisional capacity in that they are exclusively cognitive in nature and rely on objective facts. They do not pay sufficient attention to pathologically-induced changes in values that may impair decision-making capacity and they ignore the positive contribution of emotion to capacity.[cxi] Dalpe et al identified the need to consider the inherent limitations imposed by capacity assessment tools, and that an important area for future work is to develop, validate, and implement different capacity assessment tools for different high or low risk research contexts.[cxii]

Vulnerability and voluntarism

While there has been a move away from labelling groups as vulnerable, there may be characteristics resulting from an individual's circumstances that lead to considering someone as vulnerable. For example, coercion and undue influence may arise through dependency, affecting an individual's decision to participate in research and the expression of their personal values. Dependency could be on family members who may compromise a person's ability to refuse to participate in research or on a medical service (e.g. a person may feel they can't refuse if enrolled through their physician).

Recognising the principle of voluntarism as fundamental to informed consent, special scrutiny should include an evaluation of potential negative influences to mitigate involuntary commitment.

Roberts described four domains of potential influence that researchers could use to assesses voluntarism, understanding that voluntarism is a dynamic concept and that any analysis should be mindful of how these come together meaningfully within a person:[cxiii]

- *Developmental factors*: cognitive abilities, emotional maturity, and moral character.
- *Illness-related considerations*: symptoms associated with mental or physical illness may serve as negative factors that seriously detract from voluntarism e.g. if a person experiences ambivalence and indecisiveness, poor energy, negative thoughts, an inability to read one's own internal emotional state and preferences, impaired insight and judgment and/or physical pain.
- *Psychological issues and cultural and religious values*: an individual's cultural and religious values may affect how symptoms are perceived, how illness is defined, and whether consenting to an intervention is acceptable.
- *External features and pressures*: including a lack of resources in the person's normal health care setting meaning they have a lack of viable alternatives and the coercive influence of professionals, family or caregivers or of the decisional process itself.

Researchers and RECs have a role to play in determining if influences on voluntary consent cross the threshold of being undue, and if so, which safeguards are appropriate.[cxiv] This will vary not only in relation to the person's personal characteristics and situation but also on the nature of the decision they are being asked to make (e.g. greater certainty of a decision being voluntary should be required for more complex or risky research). Those involved in recruiting participants need to be trained to recognise, and empowered to respect, a potential participant's 'silent refusal'.[cxv] However, this raises a question about the extent to which, in difficult to judge and measure contexts, a decision should rely on either or both the integrity and internal moral compass of researchers, and/or that of formal assessments.

The potential for vulnerability can be especially acute in humanitarian settings (e.g. refugee camps and conflict zones).[cxvi] In research conducted in an unstable and political environment vulnerability arises from unequal power relations within a community, and between a community and various authorities. However, research is crucial as the mechanisms by which mental health problems might be averted or precipitated in humanitarian settings is not fully understood.[cxvii]

Even under politically stable conditions, there may also be systemic injustices and/or historical prejudices that influence the decision of participants to consent to participating in research, for example in extreme poverty where anything is better than nothing, especially with regards to families struggling to cope with persons living with mental health conditions. It is important for researchers to recognise that disempowerment and marginalisation enhance other vulnerability factors e.g. non-literate, poverty, intimate partner violence, etc. which are not specific to mental health problems but are enhanced by mental health problems.

In some settings, there is also a question of class where illiterate or marginalized groups might have shown a predisposition of servitude towards researchers or may even just feel happy to have been considered by researchers—especially foreigners from HICs—as worthy of being studied.

Stigma leading to discrimination and abuse

What is the ethical duty of researchers to assess and address mental health stigma as part of their research?

What approaches can be used to aid cultural understandings of stigma towards those with mental health problems (e.g. research methods, co-design approaches etc)?

What strategies can researchers adopt throughout the research process to mitigate or address mental health related stigma (including how research is conducted and specific interventions to reduce stigma)?

Globally, stigma is greater in relation to mental ill-health, than physical ill-health, and can result in discrimination and low social integration of individuals with mental health problems. In this context, research participants may be vulnerable to stigma through their participation in mental health research. The potential for research to prompt and exacerbate stigma-related discrimination should be considered during the research design e.g. if a researcher conducts house visits these could take place 'out of hours' to prevent others from noticing the researcher's presence.[cxviii] Confidentiality and privacy are of critical importance to avoid increasing participants' vulnerability to stigma and community rejection. In addition, telling the person they have a 'mental disorder' has a potential for harm e.g. if the person externalises the reason for their symptoms (perhaps linked to social adversity), attributing to an individual illness could undermine coping and worsen the person's situation. However, in some cases, a researcher's interest in person's living with mental health problems could actually reduce stigma, for example, when the researcher's attention makes that person suddenly become worthy within a community that stigmatizes her.

Social attitudes may prevent individuals from seeking to be part of research or not understanding that the research could be relevant to them. Research by Maulik et al investigating a mental health services delivery model using technology-based solutions for rural India and found that at times the economically well-off community members refused to provide data believing that mental illness affected only the poor.[cxix] An anti-stigma campaign was conducted during this study to sensitise the community to mental health issues. Community leaders felt that those with mental health problems and even their families were often subject to stigma and discrimination and this can be a barrier to seeking treatment as they are concerned about social implications e.g. difficulties in securing matrimonial alliances for their children.

Mental health literacy and awareness raising are often a core approach to anti-stigma campaigns globally. This corresponds with the idea that once a person is 'literate' in the language of mental health, then there is greater understanding and stigmatising attitudes disappear. However, it should be recognised that people across LMIC and HIC contexts will use different explanatory frameworks and language to explain mental health problems. For some, certain language and attitudes may be regarded as stigmatising because they don't fit the 'accepted' explanatory framework, and thus people are 'illiterate' in the specific language of mental health. For example, in Africa, there is a drive to increase mental health literacy, but this presupposes that people will embrace certain language and if they do not they are considered illiterate. It is important for researchers to recognise these differences and that the imposition of an 'accepted' framework and language may devalue and perhaps even stigmatise alternative world-views that explain mental health problems in some other way. However, these differences should not result in inaction or exclusion from research. Researchers need to find ways to communicate with people, who may have a range of beliefs about the cause of their mental ill-health, and provide information that enables them to exercise their autonomy and make informed choices.

It has been proposed that more research and culturally sensitive approaches, at individual and community levels, are needed to foster greater awareness and understanding of mental health problems.[cxx] A systematic review of effective interventions to reduce mental-health-related stigma and discrimination found that most of the research has taken place in HICs, with few studies conducted in LMICs.[cxxi] Weinberg et al identified the needs for longitudinal studies to address behaviour change around discrimination, recognising that the current evidence is insufficient to determine what interventions are effective and feasible, how best to target key groups such as health care staff, and how to adapt such interventions in specific contexts.[cxxii]

The issue of stigma reduction is not only relevant to the people with mental health problems but also to those who undertake research and provide care in this field. A study by Agyapong et al examined stakeholder views about the factors that influence career choices and retention of community mental health workers (CMHWs) in Ghana. They found that vast majority of stakeholders including CMHWs, psychiatrists and health policy coordinators believed there is stigma associated with working in mental health. About half of the CMHWs interviewed said they have been impacted by the stigma in mental health, and one in five CMHWs reported that they have considered leaving the mental health profession because of stigma. Stigma can prevent young people from selecting these specialties which has the impact of further exacerbating the human resource shortage.[cxxiii] Stigma in funders and researchers may also negatively impact the field of mental health research, for example, if it prevents the prioritisation of research or results, or leads to research being conducted that systematically excludes people with mental health problems leading to a poorer evidence-base for their care.

Additional risks

In addition to risks associated with decisional capacity, voluntarism and stigma the following risks may also apply depending on the nature of the research and the research participants:
- *Placebo-controlled trials* are widely used for testing the efficacy of new pharmacological treatments but the ethics of using placebo when there is a standard, efficacious therapy have been questioned. Treatments for some mental health problems vary in their effectiveness from patient to patient. Additionally, research has shown that patients who have panic attacks, mild to moderate depression, or generalized anxiety problems get almost as much relief with placebo as they do with conventional treatment (about one-half improve with placebo).[cxxiv] This makes the scientific case for using placebo particularly strong, even though the risks of doing so (e.g. in terms of a relapse of depression) may be high.
- *The need to "wash out"* any drug a participant is already taking before testing the experimental treatment, which may induce the return of mental illness in order to test a drug that may or may not relieve it.
- *Suicidality* and how best to manage this within the context of the study and the resources available within a country's mental health system.
- *Lack of adherence* i.e. if a participant is not able to follow the study processes of taking medications as scheduled, avoiding anything contraindicated, completing visits and procedures, especially for safety assessment.[cxxv] There are also risks of researchers failing to learn what they are being told as a result of lack of adherence i.e. whether someone is unable to adhere, or if there are other incentives for non-adherence.[cxxvi] Researchers need to understand the complex social and economic structures through which adherence is modulated, and, understanding this context, put in place effective strategies to promote adherence.

- *Coordination with existing referral services or treatments*: Researchers have a responsibility to coordinate with existing services to network the research into these and ensure the services have capacity to receive increased referrals due to the research detecting more people needing help. However, even where this has taken place problems may be experienced. A study by Likindikoki et al investigated an integrated intervention to improve mental health and reduce intimate partner violence among Congolese women in Nyarugusu Camp, Tanzania. Although the camp had referral services in place these were not always available when research participants were referred for mental health issues. The study therefore continued follow up with these women to ensure their safety and wellbeing.[cxxvii]
- *No planned follow-up or treatment:* In Singapore, a non-governmental organisation is engaging in mental health promotion and research with migrant workers using mobile-based interventions for conditions like depression but there is no intended follow-up or access to medical treatment. This raises a question regarding the ethics of developing low cost digital interventions where there is no intended follow-up.[cxxviii]
- *Secondary findings of mental illness* e.g. screening questionnaires that "accidentally" pick up signs of suicidal ideation or depression.
- *Undue inducement* due to payment or the opportunity to have a health assessment and receive treatment that may not be available outside of the research study. However, the risk of inducement needs to be balanced against risks of harm and exploitation by offering too little and some would argue that payment is justified in terms of lost earnings or other expenses associated with participation.

5. Governance

Are current ethics governance structures and processes fit for purpose to support the inclusion of people with mental health problems in research?

A number of international guidelines provide principles and values to guide research with people who have mental health problems and who may lack capacity (see table below). In addition, countries will need a variety of governance mechanisms to guide and support inclusive research, including mental health laws and policies with specific provisions for research participation. Such a governance framework will need to take account of principles of equity, justice, fairness and respect for participants and balance benefits, interests and protections. It will need to address:
- inclusion where the autonomy and self-determination of people with mental health conditions are recognised and protected to counter the blanket assumption of non-capacity
- inclusion of those with mental health problems in research, to ensure findings are generalizable to all
- the right of those with mental health problems to be heard and included in priority setting, research design, and research conduct
- issues of contextual priorities at country / regional level that respond to capacity of health systems and any cultural elements
- sound research design – including addressing issues of validity / relevance of mental health diagnosis and assessment tools in diverse cultural contexts
- requirements for consent, assent, and dissent for those who lack capacity
- principles, criteria and processes for capacity assessment, including who should undertake the assessment, when and with what regularity
- provisions for supported decision-making or for surrogate consent, including who can take on this role and if/how their authority needs to be established and procedures for implementing advance directives in research (see below)
- provisions for protecting persons from coercion and undue influence

- mitigation of risks of harm to participants from stigma-related discrimination and abuse
- protection of privacy and confidentiality
- ethical review processes and what extra safeguards should be in place for people who lack capacity (see below)
- how conflicts of interests will be managed e.g. if the person assessing capacity are also the people recruiting to a study.

However, there are many challenges to achieving an ideal governance framework including, in some settings, achieving the necessary government buy-in. Without this there may be a failure to implement relevant laws and policies leading to a lack of local guidance for researchers and RECs.

Ethics of involving people who can't consent: surrogate consent

What regulatory models do different countries use to include people who lack capacity to consent (e.g. who decides on behalf of the individual; is a lasting power of attorney or an advance directive possible or applicable to research consent; are the courts involved in appointing a surrogate decision-maker; is this decision-maker legally recognised or recognised 'in practice' (e.g. a family member); does the model promote inclusion or increase the likelihood of exclusion?)

Does a country's governance structure and regulation support or challenge the ability to conduct research with people who have mental health conditions and lack capacity (e.g. in relation to how capacity is defined and the provisions (if any) for surrogate decision-making?

The CIOMS guidelines articulate a number of provisions for surrogate consent for situations where an individual is not capable of consenting for themselves (Box 2). How these guidelines translate into practice, and the models adopted by different countries, are likely to vary. For example, some countries may have legal tools that permit an individual to make an advanced directive indicating their future wishes, including who should act as their proxy if they lose capacity in future. This legally authorized representative (LAR) (e.g. a family member) is responsible for considering the preferences and wishes of the individual and conveying what they would likely have chosen had they had capacity. In the absence of a directive, and where no-one is available or willing to act in a personal capacity, a professional LAR (e.g. a doctor responsible for the person's care) may be appointed. However, the scope of laws for surrogate consent are often limited to certain types of decisions (e.g. health care treatment), and their application in research contexts can be uncertain, with a lack of clarity about who (if anyone) can act as a LAR for research.[cxxix] It is also possible for surrogate decision-makers to be recognised in practice, if not in law, for example where decision-making passes naturally to a family member without the involvement of the courts.

> **Box 2. CIOMS international ethical guidelines: permission of a legally authorised representative**
>
> In accordance with relevant national regulations, the permission of an immediate family member or other person with a close personal relationship with the individual must be sought. Surrogate decision-makers must evaluate to what extent study participation is consistent with the individual's previously formed preferences and values (if any), and, in the case of research that offers participants a prospect of clinical benefit, to what extent study participation promotes the individual's clinical interests. Previously stated preferences regarding the individual's willingness to enrol in research or documented preferences in an advance directive should be respected. Researchers must recognise that surrogates may have their own interests that may call their permission into question. Furthermore, in situations where a legally authorised representative is not available to allow for timely enrolment, researchers may obtain the permission of a representative who is socially accepted but not formally recognised before the law.

Some countries may lack the legal provisions for nominating a LAR, with decisions falling instead on the common law and a doctor's determination of best interest. This could result in researchers not being willing to take the legal risk because there is no legally recognised representative in the governance structure. Where this leads to the exclusion of those who lack capacity it may result in less meaningful research and unjust exclusions from research. Other countries may have legal provision that make surrogate consent theoretically feasible but the mechanisms required to put this into place do not exist leading to exclusion.

Mental health law and regulations on capacity in many countries focus on protecting people from themselves and protecting others who may be at risk. Many countries do not distinguish between capacity in this context and capacity to participate in research, even though the paradigms are very different. Regulation and governance structures need to find the right balance between protecting participants and advancing important research that addresses the health needs of this population, while supporting the individual's self-determination. For example, people who lack capacity should have the right to be supported – or at least involved in – decision making and their assent should be sought and their dissent respected, even if formal consent is provided by a LAR.[cxxx]

Finding the right balance on capacity is difficult and well-meaning legislation may have unintended consequences. For example, in Argentina, historically, LARs were determined by law. More recently, implementation of the Convention on the Rights of Persons with Disabilities sought to increase the autonomous decision-making of persons with disabilities so they can participate in research only if they give their own consent, with the support of a third party, if required, to exercise their rights. The potential participant can also appoint a proxy to make a research participation decision, or a proxy can be obtained by judicial process. Difficulties have ensued where a person lacks capacity to consent and there is no prior determination of a proxy by the individual or by court order. While this situation is common, it has resulted in the Regulatory authority not approving clinical trials that recruit this population and only early stages Alzheimer's disease studies are being approved. Moreover, if a participant loses capacity to consent during the trial, his/her participation must be discontinued.[cxxxi] This demonstrates the complexity of surrogate consent mechanisms and finding the balance between protection of the individual and their autonomous decision-making, and the advancement of research.

Ethics review and oversight

The ethics review process for research involving individuals with mental health problems may require additional scrutiny, including:
- whether inclusion/exclusion criteria are justifiable
- whether capacity assessment is required and, if so, how this was undertaken, by whom, and how frequently (e.g. in cases of fluctuating capacity)
- protocols for how the best interest of the participant will be established
- provisions for fully informed consent, and where required surrogate consent
- the involvement of experts by experience in the design of the research
- safety procedures for making mental health referrals (including the capacity of health systems to respond to these), and for responding to changes in mental health status that may require additional treatment support
- the training and skills of the research team for responding to potentially distressed or impaired participants
- how RECs based in HIC can best be equipped and informed to assess contextual considerations (e.g. individual, family and community level risks of mental health stigma /

discrimination; contextual appropriateness of certain types of questions – such as relating to suicide)[cxxxii]
- addressing access to research benefits, particularly in the development of new pharmacological or technological treatments that may have commercial value.

There is also an open question as to whether RECs should have an added duty to audit and actively monitor research that involves people who have limited or no capacity to consent.

From a research ethics perspective there is a need to remain critical of an 'exclusion to protect' approach that may prevail in the ethics review process leading to the exclusion of individuals with mental health problems from research. Involvement of experts by experience and of mental health professionals on RECs could bring valuable perspectives to the review process.

Some research will also require oversight by a Data and Safety and Monitoring Board to review adverse events throughout the research. For example, where research involves very vulnerable people e.g. suicide risk. The role for such a board should be commensurate with the level of risk posed by the research and should recognise the duty of the researchers to assess and respond to these issues on a day-to-day basis.

International initiatives and capacity strengthening

The need for capacity strengthening in mental health research has been identified, in addition to the need for incentives for young researchers (e.g. career pathways, training opportunities etc). Issues of training cut across all of the thematic areas addressed in this paper, including epistemology, methods, policy engagement, public engagement, role of language, building effective partnerships, co-creation of research and valuing diverse voices with a stake in the research topic. Training and capacity strengthening are essential to build and maintain robust governance structures.

Key institutions and initiatives conducting or supporting research and providing capacity strengthening opportunities include:
- National Institute of Mental Health – funded five research hubs[cxxxiii] and additional scale-up hubs in LMICs.[cxxxiv]
- The Mental Health Innovation Network (MHIN), with two new regional hubs – MHIN Africa and MHIN Latin America and the Caribbean[cxxxv]
- Grand Challenges Canada's Global Mental Health program[cxxxvi]
- Centre for Global Mental Health – several research projects across a broad range of LMICs (e.g. PRIME, The Friendship Bench, TENDAI, PROACTIVE, AFFIRM, PREMIUM, EMERALD)[cxxxvii]
- The African Mental Health Research Initiative (AMARI)[cxxxviii]
- Johns Hopkins Bloomberg School of Public Health who have helped establish the evidence base around LMIC task-shifting in mental health.
- Wellcome[cxxxix]
- UK Research and Innovation[cxl]

Relevant International Guidelines

Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (CIOMS/WHO) (2016). *International Ethical Guidelines for Health-Related Research Involving Humans*. https://cioms.ch/wp-	Sets out universal ethical principles to be upheld in the ethical review of research protocols. See Guideline 16 – Research involving adults incapable of giving informed consent

content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf	
Council of Europe (1997). *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine*. (Oviedo Convention) https://rm.coe.int/168007cf98	Legally-binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances. Contains general, applicable provisions and provisions specific to adults who have mental health problems and those not able to consent. See Article 6 – Protection of persons not able to consent and Article 7 – Protection of persons who have a mental disorder**.**
Council of Europe (1999). *Recommendation No. R (99) 4 on Principles Concerning the Legal Protection of Incapable Adults*. https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016805e303c	Principles relating to legal arrangements and including the need to recognise different degrees of incapacity and that incapacity may vary over time and that a 'measure of protection' should not automatically deprive the person concerned of the right to consent or refuse consent to any intervention in the health field when his or her capacity permits him or her to do so.
UN Educational, Scientific and Cultural Organization (1997) *Universal Declaration on Human Genome and Human Rights* http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/	Articulates principles and value concerning human dignity and the human genome. See Section B Rights of the persons concerned for comments on persons who do not have capacity to consent.
UN Convention on the Rights of Persons with Disabilities https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities.html	The purpose of Convention is to promote, protect and ensure the full and equal enjoyment of human rights by persons with disabilities. Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments. See Art. 12 - Equal recognition before the law, exercise of legal capacity.
Inter-Agency Standing Committee Recommendations for conducting ethical mental health and psychosocial research in emergencies (2014) https://interagencystandingcommittee.org/mental-health-and-psychosocial-support-emergency-settings/documents-public/iasc-recommendations	Provides recommendation to ensure ethical principles and to promote standards of best practice for mental health research in emergency settings.

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