OPEN LETTER

Ethics review of multicenter neuro-psychiatric & neurodevelopmental genetics research protocols: a case study of the NeuroDev & NeuroGap-Psychosis studies [version 1; peer review: 2 approved with reservations]

Telahun Teka Wolde¹, Rosemary Musesengwa², Andrea Palk³, Erisa, S Mwaka⁴, Violet Naanyu⁵, Adamu Addissie⁶, Getnet Tadele⁷

¹Department of Pediatrics, Ministry of Science and Higher Education, Addis Ababa, Ethiopia

²Department of Psychiatry, University of Oxford, Oxford, Not Applicable, OX37JX, UK

³Department of Philosophy, Stellenbosch University, CapeTown, South Africa

⁴Department of Anatomy, College of Health Sciences, Makerere University, Kampala, Uganda

⁵Department of Sociology Psychology & Anthropology, School of Arts & Social Sciences, Moi University, Eldoret, Kenya

⁶Addis Ababa University, School of Public Health, Department of Preventive Medicine, Addis Ababa University, Addis Ababa, Ethiopia

⁷Department of sociology, Addis Ababa University, Addis Ababa, Ethiopia

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Abstract

Complex research such as neuropsychiatric genetics presents unique challenges for research ethics committees (REC), particularly in Africa where genetics research on mental & neurological disorders is still in its infancy. To reflect on these experiences of reviewing Neuropsychiatric Genetic studies we use two multicenter studies, the NeuroDev and NeuroGap-Psychosis studies.

We explored the content of the national guidelines and regulatory frameworks and the processes for ethics review in the participating African countries, to identify regulatory challenges, and to recommend areas for improvement. We also held reflective discussions with REC members involved in the review of the two studies were interviewed discussing their experiences of reviewing the two studies from the point of view of an African REC/REC member who reviewed the studies.

Across all sites, a distinct theme was that the RECs did not have adequate knowledge and expertise for reviewing genetics and genomics studies in general. The review of guidelines showed the need to proactively update guidelines to meet the increasing complexity of research, ensure awareness creation, and continual capacity building of REC members.

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Keywords

Ethics Review, Genetics, Genomics, Ethics Guidelines, Research Ethics Committees, IRB

Corresponding author: Rosemary Musesengwa (musesengwa@gmail.com)

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Introduction

The global burden of mental and neurological disorders has increased significantly in the last few decades (Whiteford *et al.*, 2015). In low- and middle-income countries (LMICs), these disorders represent a total of 19.1% of all disability to health conditions (Evins *et al.*, 2019). Whilst progress has been made in the development of effective interventions there is still a lot to be learnt about etiology and diagnosis. There is, however, increased understanding of the major role played by genetic factors in most mental and neurological disorders (Forero *et al.*, 2014). Genetic studies have the potential to identify specific sensitive and susceptible genes and their interactions, and may indicate presence of, or risk for, disease/s, thereby eventually paving the way for more effective treatments (Premoli *et al.*, 2019).

Neuro-psychiatric genetics studies may provide significant insights into the complex etiologies of neuropsychiatric disorders. These studies may also lead to future benefits including screening and more targeted treatments, or even possible prevention of certain disorders. However, a cursory review of neuro-psychiatric genetic studies conducted thus far shows that the samples included in such studies have been predominantly from populations with European ancestry (Stevenson *et al.*, 2019). The inclusion of African populations in genetic research has a strong biological rationale. It is believed that modern humans originated in Africa and subsequently migrated to other parts of the world. Therefore, modern African genomes are characterized by a unique pattern of variation as a result of migration and admixture in earlier generations as well as recombination, natural selection and mutation. African genomes also have informative alleles which are useful for fine mapping of diseases causing alleles (Campbell & Tishkoff, 2008; Raychaudhuri, 2011). It is important, therefore, to include African population groups in such research.

To date, there have been no large-scale studies on the genetics of neuropsychiatric disorders in African populations. Therefore, engaging African scientists in conducting genetic studies on African populations will contribute to closing the gap in research and may reduce the inequities in mental health outcomes between Africa and the rest of the world. Population studies of genetic and environmental risk factors for neuropsychiatric disorders in Africa, through large-scale sample collection and analysis, will lay the foundations for future advances in science and therapeutics applicable to African populations (Dalvie *et al.*, 2015; Stevenson *et al.*, 2019).

This complex research presents some unique challenges from a regulatory perspective, particularly in Africa where genetics research on mental & neurological disorders is still in its infancy (Moore *et al.*, 2017).

Traditionally, Research Ethics Committees (RECs) face challenges of diversity of membership, scarcity of resources,

insufficient training of members, inadequate capacity to review and monitor studies, and lack of ethics guidelines and accreditation (Silaigwana & Wassenaar, 2015). These shortcomings negatively impact the quality of reviews and review timelines (Abbott & Grady, 2011). Review of complex research, such as neuropsychiatric genetic studies, poses distinct regulatory challenges for RECs that review such studies. A distinct challenge is lack of requisite knowledge and expertise for reviewing genetics and genomics studies in general. In addition to this, most African countries have broad and/or vague national and/or institutional ethics review guidance documents and regulations for genetics and genomics research (Ramsay *et al.*, 2014).

In 2017, four African research sites in Ethiopia, Kenya, South Africa and Uganda commenced two important research studies; the Neuropsychiatric Genetics of African Populations-Psychosis (NeuroGap-Psychosis) (Stevenson *et al.*, 2019) and the Phenotypic and Genetic Characterization of Neurodevelopmental Disorders (NeuroDev) (de Menil *et al.*, 2019) in collaboration with the Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard (Massachusetts, USA). In addition to their scientific aims these studies also aim to improve and achieve equity in mental health by expanding infrastructure and research findings and to enhance neuropsychiatric genetic research capacity in Africa through the training of scientists and supporting institutions.

In addition to funding the two studies, the sponsors also set up an independent advisory group: the Africa Ethics Working Group (AEWG). The AEWG is an international and interdisciplinary network interested in the ethics of mental health research, including experts in neuro-ethics, psychiatry, psychology, mental health, bioethics, philosophy, social science and public health. The AEWG advises principal investigators (PIs) and other research team members on ethical challenges in the NeuroGap-Psychosis and the NeuroDev studies. The AEWG builds capacity in both research and training within the ethics of neuropsychiatric genetics and genomics by publishing articles, ethical guidelines and delivering training.

While genetics and genomics research on mental and neurological disorders is crucial to Africa, it is equally important that these studies undergo rigorous review not just for scientific integrity, but also to ensure that they adhere to the highest ethical standards. These two important studies, however, elicited some ethical reflection and questions with ethical implications:

- *Are current ethics review guidelines appropriate and adequate for reviewing neuropsychiatric genetics studies in African contexts?*
- *What are the experiences of African RECs/REC members who reviewed the NeuroDev and NeuroGap-Psychosis studies?*

To reflect on these questions, as well as to contribute towards facilitating high quality future ethical review of neuropsychiatric genetic research protocols, we utilized these multicenter study sites to elicit the experiences of RECs members while reviewing the NeuroDev and NeuroGap-Psychosis studies. In addition, we explored the content of the national guidelines

and regulatory frameworks, as well as the processes for ethics review in the participating African countries, in order to identify regulatory challenges, and to recommend areas for improvement.

Are current ethics review guidelines appropriate and adequate for reviewing Neuropsychiatric Genetics studies in African contexts?

In order to review the regulatory environment, we focused primarily on the identification of ethics review guidance documents that were in use in the four countries during the review of the two studies. We sourced ethics documentation from the REC websites, the [International Compilation of Human Subjects Standards](#) compiled by the US Office of Human Research Protections, and the [Health Research Web](#) (HRWeb). In total, nine documents were included in the review i.e., 3 Acts and 6 guidance documents. We only reviewed the documents that the RECs reported were currently being used. The Acts reviewed were published between 2001 and 2012. The guidance documents reviewed were published between 2004 and 2015. We also listed the designated authorities that administer these guidelines and Acts.

In general, document review showed that the guidance that is provided for RECs to use need regular review in order to keep up with the pace of advances in scientific research. The RECs in each country have overarching guidelines that set standards, principles and values for the review of health research. Kenya has guidelines for *Ethical Conduct of Biomedical Research Involving Human Subjects* published by the National Council of Science and Technology (NCST) NO. 45, 2004 ([NCST, 2004](#)). These guidelines capture issues of vulnerable populations including mental health, confidentiality and material transfer agreements (MTAs). In Uganda, the RECs use the *Ugandan National Guidelines for Research involving Humans as Research Participants* ([UNCST, 2014](#)). It has provisions for use of stored human materials for future research; data ownership, sharing and result dissemination; and community engagement, not specific for genetics/genomics. In South Africa the National Health Research Council (NHREC) published the second edition of the national guidelines, *Ethics in Health Research: Principles, Processes and Structures*. Chapter 3 includes some discussion about ethical areas relevant to genetics and genomics research in general, including guidance about collection and storage of biological materials and data. Ethiopia's national guideline (5th edition) is much more succinct, and it includes a chapter on genetics studies that give an overview of directives about biological samples, the procedure to be used to obtain samples, and the type and size of samples. The guidelines also state that the collection, processing, handling, storage, transfer, and destruction of human biological materials and data should be conducted in a manner that protects the privacy of research participants and the confidentiality of their specimens and data. In addition, the guidelines indicate that: a) the participant should get ample information on informed consent processes with regard to genetics research and that investigators should get access to individual health information, b) the participant

should be given the option of allowing samples to be shared or not, and all secondary and third party uses of biological samples should be restricted to anonymized samples c) procedures should be in place if the participant requests that their sample be destroyed or stripped of identifiers, d) there should be a statement asserting that the study is for research purposes only, and that no individual results will be given back to study participants, and e) participants' information including research results, will not be given to family members, employers or other third parties without written permission of participants and Ethics Committee approval.

What are the experiences of African RECs/REC members who reviewed the NeuroDev and NeuroGap-Psychosis studies?

In as much as we had done a document review, we also held informal discussion with either members of the RECs and/or ethics experts who had been involved in the review of the two protocols. This was for us to understand that the actual experience of being asked to review complicated and novel protocols. The members highlighted the following challenges with the review process; limited expertise among ethics committee members within the field of genetics; lack of clear reference to genetics issues in the guidelines; limited capacity for REC to monitor future studies; adequacy of consent for complicated research; feedback of findings to families; privacy and confidentiality for families; ownership of biological samples; Intellectual Property (IP) rights; consent for future unknown studies; consent for transfer of materials; challenges in translating technical or scientific terms such as “genes” into local languages; provision of feedback of emergent findings to source communities during the study period and in the future, and determining sharing of future emergent benefits.

Discussion

This exploration of the review process and pathway of the NeuroDev and NeuroGap-Psychosis studies was conducted to describe the ethics review pathway, explore the unique challenges that the RECs faced when they reviewed the two studies, explore the guidance available to RECs for reviewing such studies, and to potentially identify any gaps in the review systems or guidance documents.

REC approval pathways

In all four countries the REC approval pathways for the review of the studies revealed either a one or two tier-system. In South Africa the studies are only reviewed by the Institutional REC. In Kenya every research institution is required to have an ethics review board or committee (IREC/IREB) accredited to the National Commission for Science, Technology and Innovation (NACOSTI). These boards/committees vary (by name and function) from institution to institution. The common practice is for the RECs to serve as both scientific and ethics review boards – some implicitly, others explicitly. Ethiopia and Uganda have a slightly different two-tier system which involves institutional REC then also National Ethics Committee (NEC).

REC review challenges

The major challenge identified by the RECs pertains to lack of expertise to review neuropsychiatric genetics and genomics studies. This finding is not unique to the NeuroDev or NeuroGap studies but is a general concern of most RECs, particularly in developing countries (Hyder *et al.*, 2013; Kass *et al.*, 2007). It is never possible in any REC to have all the requisite expertise on a REC. RECs can find means to mitigate this reality by either having external reviewers or constitute ad hoc committees as required (Nyika *et al.*, 2009; Silaigwana & Wassenaar, 2015). However, review of complex research, such as neuropsychiatric genetic studies, poses distinct regulatory challenges for RECs that review such studies. Research indicates that most psychiatrists and neurologists do not have sufficient training in genomics or genetics and are not familiar with current research in their area, yet, they are the ones that RECs count on to review neuropsychiatric studies (Klitzman *et al.*, 2014a; Klitzman *et al.*, 2014b; Ward *et al.*, 2019). There is also an indication that developing subject experts in this particular area will not be easy as there is also a need to embed the genomics and genetics knowledge into the medical curriculum (Klitzman *et al.*, 2014a; Salm *et al.*, 2014).

RECs might also want to consider utilizing external reviewers for projects in which they lack expertise. Having a list of external experts in particular areas, who can be consulted when needed, will increase the capacity for RECs to review projects that need specialist advice. Literature suggests that the quality and confidence in review of a proposal will depend on whether the REC has a subject area specialist, either advising the REC or as a member of their committee (Bledsoe *et al.*, 2007; Gold & Dewa, 2005; Pritchard, 2011).

Another way of addressing these challenges is to carry out extensive capacity building of REC members in subject matters where they lack capacity (Hyder *et al.*, 2013; Mielke & Ndebele, 2004; Ndebele *et al.*, 2014a; Nyika *et al.*, 2009). The aim of these kinds of initiatives is not meant to produce a cohort of subject matter specialists, but to equip REC members to be able to articulate ethical issues in specialized protocols and therefore to build confidence in reviewing such protocols. On the other hand, building an extensive network of researchers in neuropsychiatric genetics and genomics will also increase the pool and network of reviewers on the continent (Yakubu *et al.*, 2018).

Ethico-legal framework

All the RECs identified issues in the guidelines that they felt needed to be added or addressed adequately. The availability of adequate, updated local policies and guidelines that may assist in the review of research protocols related to such research is therefore crucial. While there have been efforts on the African continent to critically analyze the guidance that is available for both review and implementation of genetics and genomics studies in general, this is not been the case for neuropsychiatric studies (de Vries *et al.*, 2017; Ramsay *et al.*, 2014). Workshop and consultations have been held with researchers, REC members and community members in order to update the guidelines and inform best practices (de Vries *et al.*, 2017; Tindana *et al.*, 2019; Yakubu *et al.*, 2018).

In contrast to the other countries, in South Africa there has been more efforts to have guidelines on genetics and genomics than the other three countries. The Academy of Science of South Africa (ASSAf) commissioned a Consensus Study on Genetics & Genomics in South Africa in December 2018, and it is likely that this study will significantly inform the update of the national guidelines. The ASSAf document also highlights the importance of community engagement in genetic studies, particularly the use of community advisory boards (CABs) comprising multiple stakeholders to afford a deeper understanding of ethical issues (ASSAf, 2018). Mention is also made of the effective use of a CAB in the context of a psychiatric genetics study that took place in South Africa (Campbell *et al.*, 2015). While neither this document nor the national guidelines discuss issues specific to neuro-psychiatric genetics studies, if proposals and protocols are cognizant of the relevant ethical issues as well as appropriately designed and written, then guidelines that pay adequate attention to the ethical issues associated with genetics and genomics studies, in general, should be sufficient in assisting RECs in their reviews. That said, genetic studies which include participants with mental disorders must ensure that special attention is paid to challenges associated with assessing capacity to consent.

RECs ethical concerns

Although the need for more genetic information on neuropsychiatric disorders is critical for elucidating the problem, the RECs identified other ethical concerns such as sample handling, informed consent, privacy and confidentiality, feedback of findings, post-approval monitoring of research, intellectual property rights, feedback of findings and sharing of future benefits. These findings actually mirror the same discussion point from a workshop of RECs that were reviewing genetics and genomics studies in Africa (Ramsay *et al.*, 2014). This indicates the need to promote capacity strengthening for RECs review of genetics and genomic projects. To address this at continent level the H3Africa consortium has been engaging with all stakeholders in genomics and genetics research to try and address these concerns, document best practices and develop Afrocentric guidance for researchers and RECs (Tindana *et al.*, 2019). The H3Africa Consortium has employed several approaches through H3Africa Ethics and Community Engagement Working Group to developing appropriate ethics and community engagement policies and guidelines (H3Africa, 2014).

Considerations elicited by African research contexts

There are some unique, contextual concerns that were highlighted by the RECs that we would like to address. Solutions to ethical issues need to be grounded within the broader socio-economic, cultural and political context of a given society or indigenous African moral systems, values, norms, thoughts, philosophy and realities on the ground (Kamaara *et al.*, 2020). In particular, where genomics and mental health intersect, many of the challenges lie in the ethical, legal and societal realm (informed consent and understanding, stigma, community engagement, fairness, privacy, vulnerability, confidentiality, equity and feedback of findings) and there is a need to address all these ethical issues by different locally

embedded policies and guidelines. Genomic research on mental illness should thus be planned, designed, and managed with the necessary flexibility in budgets and protocols to allow researchers to act on context specific emerging issues and to improvise protocols and practices based on insights from the patients and other stakeholders. This also suggests the need for intellectual ownership and autonomy by local PIs and other investigators. Thus, improvisation and flexibility are more important than universal ethical guidelines.

Neuropsychiatric genetics studies in Africa present distinct challenges in terms of translating the relevant scientific concepts and study aims into local languages for which equivalent terms may not be available. Using ‘loan-words’ or ‘like for like’ translations is an inappropriate solution to the problem of ensuring adequate understanding. (Munalula-Nkandu *et al.*, 2015; Ndebele *et al.*, 2014b). The problem is compounded by the fact that such studies are highly complex and employ specialized terms which are challenging for laypersons to grasp. In particular, ensuring that participants in low-resource contexts with low levels of education have adequately grasped the study information may present challenges (Munalula-Nkandu *et al.*, 2015). Moreover, study information that draws on a biogenetic explanatory model of disease may be at odds with local explanatory models, which may interpret illness in terms of non-materialist frameworks (Kamaara *et al.*, 2020).

Here, we conclude with what we take to be one of the primary concerns: issues related to ensuring authenticity in the consent process in low-resource contexts, in which participants have minimal education and relationships are more interdependent and hierarchical. The challenge here is that consent processes that have been designed by researchers far removed from the study sites may not be suitable for the local realities of such participants. Given that adequate understanding of the nature of the research is requisite for authentic informed consent, RECs must ensure that protocols stipulate how challenges related to translation will be addressed.

While there is considerable diversity in the beliefs, attitudes and values that comprise the worldviews of individuals living across the African continent, there is nevertheless a commonality that is the basis for describing such worldviews as more collectively orientated as opposed to individualistic (Palk *et al.*, 2020). This tendency to view the self as constituted through and with the other and situated within a community

that may extend into the past as well as the present, has implications for decision-making and thus for the consent process. RECs must ensure that protocols have made adequate provision for consent that permits deliberation with significant others and is sensitive to the requirements of shared decision-making. An example would be permitting potential participants to take information sheets home with them to discuss with others. While the need for protocols to be sensitive to local contexts is requisite for ethical research across the board, it is even more important in the case of neuropsychiatric genetics studies that include participants with neurocognitive impairments.

Last, but certainly not least, RECs must pay particular attention to studies that include conditions that are subject to high levels of stigma. While the problem of stigmatization of persons with neuropsychiatric disorders is a challenge that is not unique to Africa, it nevertheless requires careful consideration in the context of reviewing neuropsychiatric research protocols for studies that will take place in contexts where there is heightened risk to participants. In this regard, RECs must ensure that protocols include adequate prior consultation and discussion with communities in order to ensure understanding of the nature of the research, so as to avoid exacerbating stigmatizing ascriptions of the disorders that are the focus of the study.

Conclusion

Our discussion supports the need to revisit the existing guidelines, update them cautiously in tandem with evolving science, and ensure awareness creation, and capacity building among health and research institutions, researchers and communities. Researchers and institutions should take these advantages and utilize standard operating procedures of review that oversee and ensure that critical principles of research ethics are met. Finally, guidelines should be sufficiently detailed to ensure that research on the genetics of neuropsychiatric disorders is respectful of persons and their autonomy, privacy and confidentiality as well as equitable and beneficial, where possible, to participants.

Data availability

No data are associated with this article.

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Open Peer Review

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Alice Matimba

Wellcome Connecting Science, Wellcome Genome Campus, Hinxton, UK

General comments

This is a great and timely paper as there is more realisation of identifying gaps and tailoring ethics guidelines for genetics and genomics research in the African contexts. Congratulations to the authors for setting this focus of study. My comments aim to bring clarity to various concepts highlighted in the research and should be regarded upon as constructive towards improvement of the paper.

General comment 1: There is a need for consistency in the order of objectives throughout the paper, from abstract, introduction, methods and results, and discussion. Some sections start by talking about the review of guidelines, then others start with RECs experiences.

General comment 2: The main goal of the article needs to be revised to fit the results, by re-adjusting the objectives (see suggestions below). This will help to structure the methodology and the rest of the article and provide more sufficient focus around pertinent ethics issues around neuropsychiatric genetics and genomics, as opposed to general ethical issues in genomics research as is in the current state of the paper.

Specific comments

Abstract

- In reference to this statement - *To reflect on these experiences of reviewing Neuropsychiatric Genetic studies we use two multicenter studies, the NeuroDev and NeuroGap-Psychosis studies. We explored the content of the national guidelines and regulatory frameworks and the processes for ethics review in the participating African countries...* Authors please provide some context e.g. overall goal(s) of these studies in relation to genomics research to set a context.
- This statement needs rephrasing - *We also held reflective discussions with REC members involved in the review of the two studies were interviewed discussing their experiences of reviewing the two studies from the point of view of an African REC/REC member who reviewed the*

studies. Provide specifics e.g. mention the 4 African countries which were part of the studies in reference to this statement - We explored the content of the national guidelines and regulatory frameworks and the processes for ethics review in the participating African countries...

Introduction

- Authors should briefly explain the terms around mental and neurological conditions, then neuropsychiatric conditions. Authors tend to sometimes refer to mental and neurological conditions. From a layman point I assume these conditions may have related underlying etiologies, but do they have similar ethical risks as specifically neuro-psychiatric conditions, which, to my understanding could be the main disease focus of this paper. This needs clarification. Specifying the conditions and giving examples which can be related to in the African settings will help the reader to set the context of the paper. Some parts of introduction refer more specifically to neuropsychiatric conditions and would be ideal to be consistent, helping to guide the reader. Some of the more pertinent risks and issues in genomics research are around data sharing and this could be included in the introduction or in discussion as there are gaps for further exploration, but worth mentioning in this context.
- Authors wrote - *There is, however, increased understanding of the major role played by genetic factors in most mental and neurological disorders.* I believe what is meant by the referenced author is that genetics plays a major role in the risk of neurological disorders. And not that most mental and neurological disorders have been studied to give this conclusion.

Methods & Results

- The authors introduce the studies - *Africa and Uganda commenced two important research studies; the Neuropsychiatric Genetics of African Populations-Psychosis (NeuroGap-Psychosis...* Provide in brief, further summary information of the studies/projects – including e.g. types of data being generated - individual genotype data, large scale genome-wide or WGS, and how it is generally used for collected, analysed and shared. All these are evolving aspects which are key for ethics review, moving away from the traditional genetics research to more genomics approaches. That is if there was such an intention in this paper. In summary what are these studies doing and why are they relevant to this study.
- Please provide further demographics of the *Africa Ethics Working Group (AEWG)* working group in terms of their location and their how well suitable they are placed in addressing ethical issues in African settings, and the motivation to conduct this study.
- The 2 research questions do not quite align with the methods and results obtained in this paper. In fact, this does not seem to be the appropriate methodology to measure adequacy and appropriateness as this would require description of how the guidelines were produced, by whom and for whom to measure the fit or purpose done via consultations and specific measurements of in-appropriateness based on a standard or baseline. Authors have not described any baseline or standard that the adequacy or appropriateness should be measured against, and I believe this is beyond the scope of this study. However, based on the methods described in this paper and the results obtained it seems the questions could be along the following lines
 - What are the ethics review pathways for the RECs
 - What were the perceptions and experiences of RECs regarding review of neuropsychiatric genetics research

- What regulations exist and how are these applied in the pathways, and what are the potential limitations (based on a specific expectation?)

Using such a structure (upon refining) will help to have a more logical flow to the paper.

- Ethics review guidelines - Authors note that they sourced ethics documentation from websites - *We sourced ethics documentation from the REC websites, the International Compilation of Human Subjects Standards compiled by the US Office of Human Research Protections, and the Health Research Web (HRWeb)*

1. Why are these websites or documents the appropriate documents for this study? Why these, and not others? Also please expand on what are Acts and guidance, what is the difference. List or summarise the Acts and the guidance document possibly in a table - linking to next comment of providing a summary overview of the documents analysed.
2. A table summarising key findings of the guidelines will be ideal. Were these guidelines related to ethics generally or specifically to genomics research?
3. Authors mentioned that 9 ethics guidelines were reviewed, but only 4 of them are summarised. What was the purpose of reviewing the other documents and what was extracted from these - was this to set a standard of what should be included in ethics reviews generally?
4. What were your expectations or hypothesis around the ethics guidelines with the specific focus of neuropsychiatric disease research?

- Experiences of the RECs

1. How many members of the RECs were involved, what was their expertise or profiles?
2. How were the discussions done, in a meeting, how long did this take place? What specific questions did you ask them?
3. Although informal, please report a structure of how you obtained the data/information and why? Who led the discussions?
4. Did you study experiences or extracted views and perceptions?
5. An understanding of the composition of the RECs, and how the process of ethics review is done or approvals made, if any consultations are made with experts, under what conditions etc...?

Discussion

1. Authors should discuss general guidelines in neuro-psychiatric research and how this already presents challenges, then in addition, genetics/genomics adds to this complexity by creating further issues around specific themes.
2. The second paragraph in Discussion described the RECs pipeline. The methods/ approach

should be included above, and also the results of that pathway possibly summarised into a table or figure comparing and contrasting the different countries. This can then be discussed in context of the findings.

3. REC approach pathways – As mentioned above, the Ethics review pathways should be described in the methods sections, describing the methods and results of the approach used to understand the RECs pathway.
4. REC review challenges - *The major challenge identified by the RECs pertains to lack of expertise to review neuropsychiatric genetics and genomics studies....* Did the RECs identify these challenges or provided views/perceptions of what might be missing in current processes or guidelines – if indeed, how so? Authors mention having informal interviews with RECs – please describe in methods how they would have identified these challenges – was it via structured discussed on themes, a checklist etc.
5. There are ethics challenges in neuropsychiatric research regardless of whether genetics is concerned. Do you think that the additional expertise needed in the RECs should necessarily pertain to neuropsychiatry or more assessing harm, breaches of information etc... related to genetics/genomics. So perhaps understanding the methodologies of how the study will be conducted, how the information will be used and why, or shared, are most important and the capacity to assess this should lie in the hands of the ethics committees. Therefore, in the minimum, RECs should indeed have access to experts but should not expect these experts to review the ethics as they are merely subject matter experts and not necessarily ethics or social, cultural experts. What is required is empowering the RECs to be able to identify when they need expertise, and what questions to raise related to the subject topics. Development of guidelines or checklists could be effective.
6. Authors state - *RECs might also want to consider utilizing external reviewers for projects in which they lack expertise.* This is good idea. However, in addition to point above, how do you maintain consistency and assess equity so that the review process is indeed fair across different projects. Perhaps setting a guideline or checklist of items to consider for this specific type of research would be ideal, and this can be applied by REC members who may be layman at subject matter but experts in ethics who are empowered enough to be able to assess ethical and social issues objectively.
7. Ethico-legal framework - *All the RECs identified issues in the guidelines that they felt needed to be added or addressed adequately.* How did the RECs "identify"? Or did they provide their views/perceptions. The methods section indicates that the authors reviewed guidelines, not the RECs. It's not clear if the RECs are the ones who reviewed the guidelines or how they identified the specific issues, was this through probing on specific issues, or they were provided a checklist etc.. Authors should clarify this in methods or approach steps. Which is why a detailed description of the informal discussions is needed, as alluded in earlier comments.
8. Authors state - *That said, genetic studies which include participants with mental disorders must ensure that special attention is paid to challenges associated with assessing capacity to consent.* It will be ideal to discuss, in this section, ethics guidelines in context of neuropsychiatric research generally and then relating to genetics or genomics how those challenges should

be considered in African contexts, beyond the South African model. Can the genetics/genomics components be incorporated into the neuropsychiatric guidelines so that it's more linked and contextual to the disease specific research guidelines?

9. Authors state - *Although the need for more genetic information on neuropsychiatric disorders is critical for elucidating the problem, the RECs identified other ethical concerns such as sample handling, informed consent, privacy and confidentiality, feedback of findings, post-approval monitoring of research, intellectual property rights, feedback of findings and sharing of future benefits.* Following from above comments - these concerns are to a large extent generic for genetics and genomics research in Africa and already reported elsewhere. Therefore, how does this study build upon this existing knowledge specifically in the context of neuropsychiatric research and provide further concerns to address. It's possible there are other more pressing ethical concerns that are less related to genetics/genomics which could be highlighted here and compared in terms of importance or impact overall. Therefore, this section could be reduced in favour of expanding on the section below on contexts.
10. The contexts section sounds very generalised with little specifics on genomics research and data in the neuropsychiatric field. This could be expanded briefly into emerging issues around data sharing, benefit sharing, feeding back results and population stigma, who accesses and uses the data and how it is analysed and made public etc...
11. Authors state - *In this regard, RECs must ensure that protocols include adequate prior consultation and discussion with communities in order to ensure understanding of the nature of the research, so as to avoid exacerbating stigmatizing ascriptions of the disorders that are the focus of the study.* Authors could reference articles that have indicated specific issues in African contexts and how this potentially links to genetic studies, especially in sense of genomics data sharing, and the associated risks related to neuropsychiatry.

Is the rationale for the Open Letter provided in sufficient detail?

Partly

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: genomics, ethics, capacity development

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 September 2021

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Nchangwi Munung

Division of Human Genetics, Department of Pathology, University of Cape Town, Cape Town, South Africa

This paper reports on the preparedness and capacity of RECs in four African countries (Ethiopia, Kenya, South Africa and Uganda) to conduct ethics review of neuropsychiatric genetic studies. These four countries were selected because of their involvement in international neuropsychiatric genetic study (NeuroDev and NeuroGap-Psychosis studies). Based on a review of national guidelines and informal discussions with REC members in the four countries, the authors identify gaps in national regulatory support of ethics review of neuropsychiatric genetic studies in Africa, limited capacity of RECs in the participating countries to undertake such ethics review. Based on the above observations, the authors make important recommendations on how to improve REC review of neuropsychiatric genetic studies in Africa. The paper contributes to the literature on research ethics review capacity for emerging scientific fields and provide practical recommendations on the way forward.

Overall, I think the manuscript can be improved in terms of providing clarity on whether this was a planned study or just observations made by the researchers during the project and for which lessons may be shared for the benefit of stakeholders interested in neuropsychiatric genetic research in Africa. A brief description of some of the methods/approaches that were used to arrive at the recommendations made. Although this is an open letter and a designated method and results sections are not required, the introductory paragraph should provide some details on the analysis of the guidelines the processes followed for the informal discussions. My suggestions are below:

Major comments

Introduction

Page 3, Introduction: The sentence/claim "*A distinct challenge is lack of requisite knowledge and expertise for reviewing genetics and genomics studies in general*" needs to be referenced. It may also be worth acknowledging that more recently, there has been some improvement in in the capacity

of RECs to review genomics studies either through capacity building initiatives within genomics research networks in Africa and online courses like the TGHN course on *Introduction to Reviewing Genomic Research*.

The authors state that in Africa, research on neurogenetic disorders pose unique challenges especially from a regulatory perspective. Although a reference is provided, it is necessary, for the sake of readers, to specify what these unique challenges are and how they differ/compare to the ethical challenges in other types of genetics research or human genetics research more broadly. Without such information it is hard to decipher what the current manuscript adds to current knowledge on REC review of genetics and genomics studies in Africa.

The paper would benefit from a methods section. This would provide clarity on how the authors arrived at the conclusions and recommendations. It is stated that national research ethics guidelines were analysed and that informal discussions were held with REC members in the different countries. However, there is little information on the processes and methods that were used. I suggest that the authors consider including information on:

- The documents that were reviewed.
- If they were mainly national guidelines? This is important as sometimes national ethics guidelines refer to international ethics guidelines such as the declaration of Helsinki, CIOMS, universal declaration of the human genome (by UNESCO) etc. The expectation is always that where national guidelines do not directly provide guidance for a particular ethical issue RECs may refer to these international documents.
- Key items extracted from the documents and why
- The process of analysis.
- Type and nature of the informal discussions.
- Who was included in the informal discussions.
- Who conducted or led the informal discussions.

Discussion

Much of the information in this section is repetitive of what has been presented in the introduction, even in relation to subheadings (different phrasing). This makes the reading of the paper confusing. I suggest the authors restructure the paper such that there is a result section has the different subheadings in the introduction and discussion combined. Then the discussion section should focus on highlighting key findings and recommendations on the way forward.

In this section of the paper the authors should provide more info on the following:

- A list (and relevant information) of the different documents that were reviewed for each country.
- The number of informal discussions held across sites and the role of the REC members

(chairperson, scientists, lay person/community representative etc).

- A summary table of the unique challenges posed by neuropsychiatric genetic studies, whether and how the different national guidelines speak to these challenges. This may be grouped per country.

Page 5: It is recommended that RECs should make use of external expertise in the case where the required expertise is not available in the REC. Since the paper is on ethics review of neuropsychiatric genetic studies, it may be worth stating if expertise in neuropsychiatric genetic is available on the continent or at the different NeuroDev and NeuroGap sites, and for which RECs can draw upon. This is necessary because in the preceding paragraph, the authors note the limited availability of neuroscientist with expertise in genetics and genomics. In the case where such expertise is not available, the authors may suggest approaches that RECs might use to overcome the challenge. The authors already mention training of REC members in neuropsychiatric genetic studies, but are there resources or courses that REC members could turn to or would training in review of genomics be sufficient? Also, a discussion on the feasibility of such an approach may improve on the discussion.

It is stated that training of REC members in the review of genetics and genomics studies may be sufficient, but additional attention should be given to challenges associated with assessing capacity to consent. In reporting on national guidelines, the authors did not state if the national regulatory frameworks for the different countries provide guidance on assessing capacity to consent and if the existing guidance, when combined with guidance on genetics and genomics, should be sufficient?

Minor Corrections

- Abstract: Edit sentence: We also held reflective discussions with REC members involved in the review of the two studies were interviewed discussing their experiences of reviewing the two studies from the point of view of an African REC/REC member who reviewed the studies.
- Page 5, Paragraph 1 line 16: Kindly check if it should it be “neuropsychiatric genetic studies” or just neuropsychiatric studies.
- Introduction, Paragraph 2: The statement “Therefore, modern African genomes are characterized by a unique pattern of variation as a result of migration and admixture in earlier generations as well as recombination, natural selection and mutation” needs a reference.
- Introduction-Paragraph 4: “Traditionally, research ethics committees (RECs)” consider specifying that you are referring to African RECs especially as the reference provided is on RECs in Africa.

Is the rationale for the Open Letter provided in sufficient detail?

Partly

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bioethics: Genetics, infectious disease control and emerging technologies.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.