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: awaiting peer review]

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

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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 (Silaiwana & 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 inter-disciplinary 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 get ample information on informed consent processes with regard to genetics research and that investigators should get access to individual health information, and 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 ERCs 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 independent 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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