STUDY PROTOCOL

Ethical issues of involving people with intellectual disabilities in genomic research: a scoping review protocol [version 1; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background: Psychiatric genomic research is a growing field of research in Africa that is looking at epigenetics of psychiatric disorders; within which a specific focus is neurodevelopmental disorders including intellectual disability (ID). Conducting this type of research is important to identify etiologies and possible interventions or areas for further research. However, genomic research generally, and psychiatric genomic research, faces many social, ethical, cultural, and legal issues; research involving people with ID is particularly challenging. All research stakeholders - researchers, research review bodies, regulators, patient groups - generally agree that involving people with ID require several considerations, including extra protection. It is also recognized that not involving people with ID in research that is relevant to them means that opportunities to learn on specific issues including lived experiences are missed. In this scoping review, we aim to describe the range of ethical and social-cultural issues concerning involvement of people with intellectual disability in genomic research from existing literature.

Methods: This scoping review will be conducted based on the Joanna Briggs Institute guidance for scoping review and reported using the PRISMA-ScR guidelines. Iterative review stages will include systematic search of six databases (Embase, Ovid Global Health, PubMed, Scopus, PsycInfo and Web of Science core collection), screening, charting and synthesis of the data. Forward and backward citation screening will also be done for the articles included in the final review. We will include peer reviewed journal articles, guidance documents and reports. Screening and selection of studies based on the eligibility criteria will be done independently by three reviewers; conflicts will be resolved through discussion with a third reviewer and other experts.

Open Peer Review

Approval Status ✓ ? ✓

	1	2	3
version 1 11 Aug 2023	✓ view	? view	✓ view

1. **Johan Thygesen**, University College London, London, UK
Jung Won Choi, University College London, London, UK

2. **Signe Mežinska**, University of Latvia, Riga, Latvia

3. **Megan Campbell**, Rhodes University, Grahamstown, South Africa

Any reports and responses or comments on the article can be found at the end of the article.

Results: The results will be included in the scoping review publication.
Conclusions: This scoping review will identify key areas of ethical tensions and possible solutions and inform opportunities for empirical ethics studies.

Keywords
Ethical issues, Intellectual disability, neurodevelopmental disorders, genomic research, scoping review

KEMRI wellcome

This article is included in the KEMRI | Wellcome Trust gateway.

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Author roles: Chepkirui D: Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation; **Kipkemoi P**: Investigation, Methodology, Writing – Review & Editing; **Bitta M**: Investigation, Methodology, Writing – Review & Editing; **Harris E**: Methodology; **Musesengwa R**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Kamuya D**: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Intellectual disability (ID) also known as Intellectual Development Disorder, is a disorder with an onset during the development period which affects the intellectual and adaptive functioning. The intellectual domain affects reasoning, learning, judgement, and problem solving, while the adaptive function influence daily life like independent living. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1] and International Classification of Diseases 11th Revision (ICD-11)[2] characterise ID based on limitations in the two domains ranging from mild to severe and profound. It is estimated that the prevalence of ID is about 1% globally[3], with most of the individuals having the mild form of ID[2]. According to a meta-analysis by Maulik *et al.,* on population based studies, the prevalence of ID is highest among children and adolescents, and globally this is higher in low and middle income countries (LMICs) compared to high income countries[4].

People with ID and other psychiatric disorders are categorised as a vulnerable population in research. Vulnerability, however, consists of complex layers that require in-depth considerations rather than mere labelling[5]. According to Luna's framework of vulnerability, it is essential to unpack the different layers of vulnerability while identifying instances where one layer of vulnerability leads to worsening of existing ones or exposure to another, termed as cascade of layers of vulnerability[5,6]. People with intellectual disability might have several other layers of vulnerability; it is essential to examine these layers critically to minimize associated risks. Various ethical concerns related to vulnerability of people with ID have been documented including, the unclear decisional capacity to give informed consent which is dependent on severity of ID and complexity of study and the information[7,8]. Other documented issues include layers of potential exploitation (where they might be involved in research to access the health care benefits), power disparities between caregivers, people with ID and researchers; issues of guardianship and how best interests can be ascertained[9]. Specific considerations for people with ID in LMICs include issues around shared decision making (who makes what decision and how this is negotiated within families, how best interests of person with ID are safeguarded and what cultural and social dynamics inform these), and wider implications for involvement in research including consent processes and research participation[10,11]. The attraction to health care and compensations offered in research studies can make it difficult to tease out the due and undue inducement in research[9,12]. In addition, intellectual disabilities like other neurodevelopmental and psychiatric disorders face many forms of stigma.

ID is commonly caused by genetic factors; genomic and genetic research aim to identify the risk factors and possible aetiology for this disorder[13,14]. More specifically in LMICs, there is a dearth of psychiatric genome wide associations studies despite their potential to identify risk factors, aetiology, and possible treatment options for neurodevelopmental disorders[15]. As highlighted above, there are challenges with involving people with ID in health research. ID has been shown to closely co-occur with other syndromes such as autism spectrum disorder[16] and Fragile X syndrome[17], which further complicates research involvement. A commentary by de Vries J., in 2019[18] on ethical issues in genomic research in South Africa highlighted the concerns around informed consent, as the return of results is described as a sensitive issue that could further stigmatise the participants. Studies have indicated the value of genomic diagnosis for children with ID[19], however according to Lily Hoffman-Andrews[20], there is still a huge burden of variants of uncertain significance in clinically care.

This protocol outlines a planned scoping review to understand the range and types of ethical and social cultural issues that arise with involving people with intellectual disability in health research. Due to the dearth of literature from LMICs, we chose a scoping review as a first step to inform planned empirical research in this area.

Review question

The scoping review question is; what are the ethical and social-cultural issues concerning involving people with intellectual disability in genomic research? The scoping review will also answer the following specific questions;

1. What ethical issues are arise in involving people with intellectual disability in genomic research and how these issues defined/described?
2. What potential solutions for the ethical issues are provided, and which guidelines, if at all, are drawn on to inform how to respond?
3. What areas of further research or knowledge gaps are identified and what recommendations are outlined in the articles?

Methods

The proposed scoping review will follow the Joanna Briggs methodology for scoping reviews and the updated revisions of the guidance[21,22]. This included a predefined review question, proposed eligibility criteria based on population, concept, context, and key outcome, and search plans as detailed in the sections below.

Eligibility criteria

Population/participants: this review will focus on research involving; people with intellectual disabilities, adults and children; family and caregivers of people with ID and research on perspectives of researchers of studies involving people with ID. ID will be used in this study alongside other syndromes and disorders that lead to cognitive impairment. This study will exclude any study on ethical issues in genetic or prenatal screening and counselling since these are usually conducted within a clinical setting and thus beyond the scope of our work which focuses on research. We will also exclude articles on genomic research reporting ethical issues for general population and not specific to ID.

Context: Articles in English language will be included due to resource constrains within the team to do translations. There will be no limititation in year of research or publication for the articles to be screened and included. We

will do a second layer of screening where we will segregate the included articles based on the country where the study was conducted. The aim will be to focus on findings from LMICs as this will ensure the issues raised are relevant to our context in Kenya.

Key outcomes: Themes regarding ethical issues and opinions on ethical concerns when involving people with intellectual disabilities in genetic and/ genomic research. Proposed solutions to these ethical issues will be identified and reported, additionally key areas for future research and knowledge gaps reported in the included studies will be extracted.

Searches

This review will follow a comprehensive search strategy to identify literature from online databases and extensive hand searching. Key words such as 'ethics', 'principle', 'intellectual disability', 'genomic research', and their synonyms will be entered to the databases. An initial preliminary search will be conducted in PubMed focusing on the medical subject headings, then the key articles from this search used to expand the search strategy. The second stage will involve systematic search of the other databases based on adaptation of the search strategy since the indexing terms might be different. The target databases will be Ovid Embase, Ovid Global Health, PubMed, Scopus, Ovid PsycInfo and Web of Science core collection. The sample Ovid Embase search strategy is presented in Box 1 below. Articles from these searches will be exported for title and abstract screening. The last stage will involve forward and backward citation screening of the articles that will be selected for inclusion in the systematic review.

Box 1. Ovid Embase search strategy

#, Query, Results from 8 Feb 2023
1 exp ethics/ 340,930
2 (ethic* or moral* or principle* or bioethic* or bio-ethic*).ti,ab,kw., 604,546
3 1 or 2 811,263
4 exp genomics/ 136,473
5 ("human genome" or hapmap or genomic* or (genetic* adj6 research*)).ti,ab,kw. 487,244
6 4 or 5 1,604,598
7 exp intellectual impairment/ 590,396
8 ("intellectual disabilit*" or "intellectual dysfunction*" or "intellectual development disorder*" or "mental retard*" or "mental deficien*" or "cri-du-chat syndrome" or "de lange syndrome" or "down syndrome" or "Prader-Willi Syndrome" or "Rubinstein-Taybi Syndrome" or "Trisomy 13 Syndrome" or "WAGR Syndrome" or "Williams Syndrome" or "fragile x").ti,ab,kw.

Screening and data extraction

Articles will be exported to EndNote reference manager and deduplication using Systematic review accelerator deduplicator programme SR-Accelerator (https://sr-accelerator.com/#/deduplicator). These will then be exported to Rayyan for title and abstract screening. Screening will be done by the primary reviewer (DC) to assess whether they meet the inclusion criteria outlined above. A second independent reviewer (DK) will screen the included articles to verify inter-rater reliability of the process. An effort will be made to obtain full texts for articles that are unclear if they meet the inclusion criteria, expert consultation will also be done at this instance. Those included at this stage will be screened by full text against the inclusion criteria by the reviewer (DC), and 20% of these screened independently by the second reviewer (DK). Any disagreements will be resolved through expert consultation and by the third independent reviewer (RM, PK, and MB). A list of reasons for exclusion will be compiled at this stage and reported as part of the final systematic review. The results of the screening and evidence selection will be presented using the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR)[23]

Data extraction of the included articles will be done based on a piloted tool developed *a priori* (Table 1). Data extraction information will include, study design and setting, country, participant characteristics/population, data collection methods, ethical issues and how they were addressed, future recommendations for conducting such research and research gaps. The draft tool will be amended, if need be, during the extraction process.

Data synthesis and analysis

A summary of the extracted data will be presented in a table adapted from the data extraction tool. An accompanying narrative synthesis will be presented for the articles included to map out the ethical issues in involving people with intellectual disability, recommendations for further research and knowledge gaps. We will synthesise the emerging ethical issues and present the key themes in a narrative format. The findings will be presented in the final publication of the scoping review and shared through presentations in different fora.

Conclusion

This review is pivotal for research conduct in low- and middle-income countries. This is specifically important for genomic studies known for its complexity in terminology and added layers of intellectual disabilities. We aim to identify key areas of ethical tensions and possible solutions and

Table 1. Data extraction template.

VARIABLE	DESCRIPTION
Author(s), year	Author(s) and year of publication
Title	Title
Type of article	Indicate type for example, journal article, guidance document, commentary, conference notes, report, policy etc
Study design	Indicate design used to collect data on the ethical issues e.g., interviews, anthropological exploration, meetings, discussions, commentary etc
Country	Country where the data was collected or where mentioned, where the findings apply
Population(s)	Indicate the population demographics mentioned in the article
	1. Age
	2. Gender
Neuropsychiatric disorder(s)	Indicate disorders including ID, relating to the ethical issues raised e.g., Downs Syndrome, Fragile X etc
Ethical issues described	Record the ethical issues as described in the article either from findings, discussions, or conclusion sections
Proposed solutions	Indicate proposed solutions to the ethical issues raised
Knowledge gaps in addressing the ethical concerns	Based on conclusions and recommendation, indicate the gaps
Comments	Note any relevant comments relating to the article/findings/key considerations

inform opportunities for empirical ethics studies within our contexts.

Data availability

No data are associated with this article.

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Reference Source
2. Girimaji S, Pradeep A: **Intellectual disability in international classification of Diseases-11: A developmental perspective.** *Indian J Soc Psychiatry.* 2018; **34**(5): 68–74.
Publisher Full Text
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Publisher Full Text
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8. de Vries J, Bull SJ, Doumbo O, *et al.*: **Ethical issues in human genomics research in developing countries.** *BMC Med Ethics.* 2011; **12**: 5.
PubMed Abstract | Publisher Full Text | Free Full Text
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PubMed Abstract | Publisher Full Text | Free Full Text
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PubMed Abstract | Free Full Text
12. Emanuel EJ, Wendler D, Killen J, *et al.*: **What makes clinical research in developing countries ethical? The benchmarks of ethical research.** *J Infect Dis.* 2004; **189**(5): 930–7.
PubMed Abstract | Publisher Full Text
13. Morris-Rosendahl DJ, Crocq MA: **Neurodevelopmental disorders-the history and future of a diagnostic concept.** *Dialogues Clin Neurosci.* 2020; **22**(1): 65–72.
PubMed Abstract | Publisher Full Text | Free Full Text
14. Stessman HA, Bernier R, Eichler EE: **A genotype-first approach to defining the subtypes of a complex disease.** *Cell.* 2014; **156**(5): 872–7.
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15. Tărlungeanu DC, Novarino G: **Genomics in neurodevelopmental disorders: an avenue to personalized medicine.** *Exp Mol Med.* 2018; **50**(8): 1–7.
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PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text | Free Full Text

18. De Vries J, Munung N: **Ethical considerations in genomic research in South Africa.** *S Afr Med J.* 2019; **109**(6): 375–377.
Publisher Full Text

19. Bowling KM, Thompson ML, Amaral MD, *et al.*: **Genomic diagnosis for children with intellectual disability and/or developmental delay.** *Genome Med.* 2017; **9**(1): 43.
PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ? ✔

Version 1

Reviewer Report 03 November 2023

https://doi.org/10.21956/wellcomeopenres.21492.r68760

✔ **Megan Campbell**
Psychology Department, Rhodes University, Grahamstown, Eastern Cape, South Africa

Thank you for the opportunity to review this important work.

The article aims to conduct a scoping review of the key ethical and social/cultural issues impacting people with ID participating in genomics research.

The introduction provides an appropriate overview of ID; then considers the issue of vulnerability within research and how this would pertain to people with ID. It concludes with an overview of ethical concerns in genomics research and how these may impact on people with ID participating in such research.

- Considering that the review seeks to understand ethical and social/cultural issues, particularly in LMIC settings that are similar to Kenya, a short paragraph on some of these anticipated social/cultural factors and how they may impact on people living with ID and their participation in genomics research would be useful.

The article then outlines the key aim and specific scoping review questions which are well articulated.

- It would be useful to decide on whether you are addressing ethical, social and cultural issues OR ethical, social-cultural issues OR ethical, and socio-cultural issues, with a short explanation of how you are defining these. You use different terms in different paragraphs

The methods section is particularly well done with a thorough description of the planned scoping review process.

There are small grammatical errors throughout which should be corrected.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ethics of neuropsychiatric genomics research.

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.

Reviewer Report 01 November 2023

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Signe Mežinska
University of Latvia, Riga, Latvia

Thank you for the opportunity to review this scoping review protocol. I agree with the authors that the ethical aspects of involving people with intellectual disabilities in genomic research in LMIC are very important. A scoping review is an appropriate methodology for the aims envisaged by the authors. To improve the protocol, I would suggest considering the following issues:

1. The focus of the review is not completely clear. In the introduction and methodology parts the authors several times emphasize that the focus will be on LMIC. At the same time, this focus is not included in the title and research questions. It would be advisable to include the LMIC focus in the title and research questions or to explain how the focus on LMIC will be implemented. A clear focus is encouraged also by the Joanna Briggs methodology for scoping reviews especially by "PCC" mnemonic (population, concept, and context). It seems to me, that LMIC is the "context" in this case.

2. Please, reconsider the review question no. 1 "*What ethical issues are arise in involving people with intellectual disability in genomic research and how these issues defined/described?*". The question is not clear and includes grammatical inconsistencies.

3. Please, reconsider the review question no. 3 *"What areas of further research or knowledge gaps are identified and what recommendations are outlined in the articles?"* Do you mean recommendations regarding further research here? If not, then my suggestion would be to delete the second part of the sentence and formulate the question in the following form " *What areas of further research or knowledge gaps are identified?*". The topic of recommendations (if you do not mean recommendation for further research) might be included in question no. 2 which already addresses the topic of potential solutions.

4. It is not clear, whether the authors plan to include in the scoping review only primary empirical research studies published in peer-reviewed journals as it seems based on "Eligibility criteria", or also other types of articles, as mentioned in the abstract (mentioning "guidance documents" and "reports" not mentioned in the further text) and the Data Extraction Template which mentions also "meetings", "discussions", "commentaries". Additionally, do the authors plan to include reviews or meta-analyses? Will only articles published in peer-reviewed journals or also book chapters, conference abstracts and publications, grey literature etc. be included? Please clarify the type of articles you plan to include in your scoping review by providing more clear inclusion and exclusion criteria.

5. The authors mention that they will apply "extensive hand searching" additionally to the data base search. The Joanna Briggs methodology requires that hand search must be detailed, e.g., by including journal names and years searched. Please, detail the hand search you are planning.

6. In the Data Extraction Template, line 4 "Study design", it would be useful to introduce more consistent categories of study design, e.g., qualitative methods (interviews, focus group discussions, observations, ethnographies etc.), quantitative methods (surveys etc.), mixed methods etc. I would doubt whether "commentary" might be included as a type of study design (it might be a type of article, as already mentioned in the previous line). Also, "meeting" and "discussions" is not a study type.

7. Please explain what the sentence "A second independent reviewer (DK) will screen the included articles to verify inter-rater reliability of the process" in the "Screening and data extraction" part means. Do you mean title and abstract screening by the second reviewer? Why will the second reviewer screen only the included articles? How will this process allow for verifying inter-rater reliability? What if there might be different opinions regarding excluded articles?

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Research ethics, bioethics, empirical bioethics

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 27 October 2023

https://doi.org/10.21956/wellcomeopenres.21492.r68761

Johan Thygesen
Institute of Health Informatics, University College London, London, England, UK
Jung Won Choi
Institute Of Health Informatics, University College London, London, England, UK

This proposed scoping review protocol focuses on the important and complicated topic of the ethics of conducting genomics research in potentially vulnerable people with intellectual disabilities. The researchers a proposing a specific focus on the impact of this type of research within low- and middle-income countries. I believe this is a really important research subject and that the suggested methods for the scoping review are clear and appropriate and should give valuable insights to the community. I only have minor suggestions for clarifications as suggested below.

Minor:

Under review question (The wording of the specific questions could be improved).

1. move “are”, further down?.

2. Consider replacing “if at all” -> “if any”

3. Which main areas of further research/knowledge gaps and recommendations are outlined in the articles?

   Under context: The second layer of segregating studies based on the country with a focus on LMICs, is meaningful, but it was unclear to me if this was an inclusion criteria for all studies in general, or if you will analyse all studies (no matter country of origin) and then specifically consider your specific research questions, with focus on both LMIC studies and none-LMIC studies. It would be good to clarify this point.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genetics, Rare-variants, EHR

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.