In defence of South Africa's National Health Research Ethics Council guidelines on heritable human genome editing

To the Editor: Ramsay *et al.*[1] critique South Africa (SA)'s National Health Research Ethics Council (NHREC) guidelines[2] on heritable human genome editing (HHGE) and our defence of these guidelines.[3] They claim first that the NHREC guidelines 'permit' live births resulting from HHGE, which they suggest is premature and ethically unsound; and second, that there is no legal certainty surrounding HHGE in SA, particularly in relation to section 57(1) of the National Health Act 61 of 2003 (NHA). Additionally, they question the methodology and relevance of our public engagement study on HHGE policy, which explored SA perspectives.[4]

We address these critiques in three parts.

The NHREC guidelines as a future-ready framework

Ramsay *et al.*'s[1] assertion that the NHREC guidelines 'permit' live births resulting from HHGE requires careful clarification. While we agree that HHGE is not yet at a stage where its safety and efficacy would justify clinical trials, the guidelines do not impose an explicit and rigid ban. Instead, the guidelines adopt a flexible framework of ethical considerations that emphasise safety, efficacy and rigorous ethical oversight. For instance, the guidelines require that the potential benefits of HHGE to individuals and society must outweigh the associated risks and uncertainties, while safeguarding the best interests of any child born because of HHGE. This is not an unconditional approval of live births, but a structured framework of stringent requirements that must be satisfied before such applications could be contemplated. Under the current state of scientific knowledge, the NHREC guidelines therefore would not permit live births resulting from HHGE.

Although HHGE is not at a stage where live births would be permissible, the central ethical question remains whether, if certain breakthroughs were achieved – such as preclinical trials demonstrating the safety and efficacy of HHGE to prevent serious illnesses – it would then be ethical to proceed with clinical trials, including live births. Provided that rigorous ethical oversight is maintained, we suggest that in such a scenario, it would be ethical to proceed. The NHREC guidelines anticipate this possibility, providing a pathway for responsible scientific progress.

If the authors agree with this ethical stance, then our disagreement lies not in principle but in whether the NHREC guidelines should explicitly anticipate the possibility of such advancements. We argue that a proactive, future-ready approach is necessary and appropriate.

Future-ready guidelines, as established by the NHREC, are critical in advancing responsible governance by ensuring that ethical oversight mechanisms are in place and adaptable as technology progresses, thereby preventing governance delays. They foster public trust by demonstrating transparency and foresight and provide scientists with a clear framework for pursuing clinical applications, encouraging responsible innovation rather than fostering uncertainty or stagnation. These factors underscore the prudence and necessity of a forward-looking regulatory approach.

Section 57(1) of the NHA

Section 57(1) of the NHA seems to have become the focus of attention regarding the question of whether HHGE is lawful. It reads as follows – note the formatting:

'57. (1) A person may not –

(a) manipulate any genetic material, including genetic material of human gametes, zygotes or embryos; or

(b) engage in any activity, including nuclear transfer or embryo splitting,

for the purpose of the reproductive cloning of a human being.'

The qualifying phrase at the end, 'for the purpose of the reproductive cloning of a human being', is separated from subsection (b) by a line break and aligned with the main body of section 57(1), rather than being indented like subsections (a) and (b). This formatting is significant, as it indicates that the qualifying phrase applies to both subsections (a) and (b). Accordingly, the manipulation of any genetic material, as described in subsection (a), is prohibited only when it is performed 'for the purpose of the reproductive cloning of a human being'. Manipulation of genetic material for other purposes is not prohibited.

The term 'manipulate' is not defined in the NHA and must therefore be interpreted according to its ordinary meaning, which includes 'to manage or utilize skillfully',[5] or 'to use something, often with a lot of skill'.[6] As such, 'manipulate any genetic material' refers to the skilful handling, control or utilisation of genetic material. Common research practices in SA, such as isolating DNA from cells and genetic sequencing, involve the manipulation of genetic material. However, the qualifying phrase at the end of section 57(1) ensures that these practices are lawful, as they are not conducted 'for the purpose of the reproductive cloning of a human being'.

A related question arises: does the prohibition on manipulating genetic material in subsection (a) extend only to the types of genetic material explicitly listed – namely, human gametes, zygotes and embryos? This is unlikely, as the Constitutional Court has held that the term 'including' is not a term of exhaustive definition.[7] Rather, human gametes, zygotes and embryos are illustrative examples of 'any genetic material', not an exhaustive list. For instance, common practices in fertility healthcare, such as *in vitro* fertilisation and pre-implantation genetic testing, involve the manipulation of gametes and embryos. Yet their lawfulness is undisputed because they are not performed 'for the purpose of the reproductive cloning of a human being'. This reasoning would also apply to HHGE.

Ramsay *et al.*[1] fail to acknowledge the importance of statutory formatting in interpreting section 57(1) by omitting the line break and the alignment of the qualifying phrase with the main body of the section. This omission creates the misleading impression that the qualifying phrase applies only to subsection (b) and not to subsection (a). It is akin to selectively reporting results in genetic analysis that exclude critical variables, leading to erroneous conclusions. Such a misrepresentation fundamentally alters the scope and application of section 57(1).

Ethics and societal views

Ramsay *et al.*[1] argue that if the NHA does not explicitly address HHGE, this 'void' should be filled by considerations of ethics, morality and societal views. Regarding ethics, the NHREC guidelines provide an *ethical* framework for evaluating HHGE, in the present and in the context of future advancements. Regarding societal views, our deliberative public engagement study conducted among South Africans is the first and only reflection of societal views of South Africans on HHGE.[8,9] The main findings were as follows. Assuming that HHGE is safe and effective, an overwhelming majority of participants supported its use to prevent genetic health conditions and to confer immunity against tuberculosis (TB) and HIV/AIDS, while significant majorities opposed its use for enhancement purposes. Throughout the deliberations, the prevailing theme was the need to balance potential health benefits with the risks of unforeseen consequences, which is encapsulated by the following provision in the NHREC guidelines:

> 'HHGE research must have a clear and compelling scientific and medical rationale, focusing on the prevention of serious genetic disorders and immunity against serious diseases. The potential benefits to individuals and society should outweigh the risks and uncertainties associated with HHGE.'

The role of international standards

Ramsay *et al*.[1] place significant emphasis on international standards, noting their involvement in drafting World Health Organization (WHO) guidelines on HHGE.[10] While international standards can provide useful guidance, there is no single global consensus on HHGE. Positions vary widely across declarations and organisations. Moreover, the WHO guidelines appear to be less directly applicable to the SA context, as they may not fully account for its unique realities and constitutional imperatives.[11,12] Even if a general consensus holds that clinical applications of HHGE are premature, this reflects the current state of technology, not a fixed or universal principle. The NHREC guidelines appropriately anticipate future advancements in safety and efficacy, ensuring that SA remains prepared to evaluate HHGE's potential responsibly.

In SA, the Constitution – not any international standard – is the supreme authority. Unlike other constitutions, it uniquely includes rights such as access to healthcare and the freedom of scientific research, having profound implications for HHGE governance. The government is constitutionally obligated to address public health crises, such as the TB epidemic, using all available resources. If HHGE offers a future solution to confer immunity against TB, it must be seriously considered.[13,14] The right to access to healthcare is complemented by the right to freedom of scientific research.[15] This is a substantive right.[16] SA scientists have the freedom to pursue HHGE research, subject only to reasonable and justifiable limitations. The rights of persons born because of HHGE clinical trials would certainly be such a limitation[15] – hence the emphasis placed on safety in the NHREC guidelines. We suggest that the NHREC guidelines align with SA's constitutional values, ensuring that HHGE research is not left unregulated, or banned, but is conducted responsibly while safeguarding public health and scientific freedom.

Addressing specific critiques

Regarding our research group's work on the legal and ethical aspects of HHGE, Ramsay *et al*.[1] state that they 'take no issue' with our view. However, they allege that we are using the NHREC guidelines to create the impression of legal certainty where there is none. Admittedly, legal certainty *in the strict sense* of case law that interprets section 57(1) does not exist. However, the formatting and language of section 57(1) are clear: it prohibits genetic manipulation *for the purpose of reproductive cloning*, but does not extend this prohibition to other purposes, such as isolating DNA, genetic sequencing, or HHGE. Suggesting otherwise would have profound implications for genetic research.

The authors comment on our deliberative public engagement study on HHGE, where we invited participants to consider a future scenario where HHGE is safe and effective, and then posed a series of policy questions to them.[4] First, the authors argue that because HHGE is not yet safe and effective, the findings of our study cannot be used to drive legislative reform. We beg to differ. For the reasons mentioned above, we favour a proactive, future-ready approach to policy-making that anticipates possible scientific advancements. We do not confuse the present with the future; because HHGE is not yet safe and effective, the NHREC guidelines do not currently permit live births from HHGE.

Second, the authors express concern that our participants might not have understood what HHGE is. Our methodology included the following mechanisms to ensure that all participants had a reasonable comprehension of HHGE:[4,8] (*i*) persons interested in participating in our study were provided with vetted resource materials, including online videos explaining the basics of genetics and gene editing; (*ii*) they were required to complete an online assessment, achieving 100% accuracy before being considered for participation; and (*iii*) a geneticist was present during deliberations to answer technical questions. While our participants were not all-knowing, these measures ensured that they had sufficient understanding to deliberate in an informed way and make informed policy choices.

Conclusion

Our defence of the NHREC guidelines regarding HHGE should not be interpreted as an endorsement of the NHREC guidelines in general, some aspects of which are problematic, as was the consultation process. However, in relation to HHGE, they reflect a proactive and balanced approach that responsibly anticipates future scientific developments while safeguarding public health and constitutional values.

By proactively addressing the potential of HHGE, the NHREC guidelines position SA to lead in responsibly advancing genomic science while upholding constitutional imperatives such as access to healthcare, freedom of scientific research, and the best interests of the child. They strike a balance, ensuring that HHGE research is neither unregulated nor unnecessarily hindered, thereby safeguarding the public interest while fostering innovation and addressing pressing public health challenges.

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Response to: In defence of South Africa's National Health Research Ethics Council guidelines on heritable human genome editing

To the Editor: The repeated attempts by Thaldar *et al.* to establish heritable human genome editing (HHGE) as legal, ethically acceptable and aligned with South African (SA) cultural values are scientifically premature, ill-informed and dangerous. In their response to our editorial, they rely on rigid, legal technicalities to achieve their argument that HHGE is already legally permissible. We did not ignore the importance of 'statutory formatting' in our editorial, but – as we pointed out – recognise that such formatting in itself does not determine the legality or otherwise of new scientific practices. To reiterate our argument: while the concept of HHGE was not yet conceived when the legislation was drafted, the intent is clear in that the outcome of live human births following genetic manipulation (as would be the case for HHGE) should not be permitted. As with human reproductive cloning (referred to in section 57(1) of the National Health Act No. 61 of 2003),[1] there is no indication that HHGE will become a reality, and it is irrational to claim that HHGE could fall into the same category as *in vitro* fertilisation (IVF) and other common practices in fertility healthcare. We are not alone in our perspective: on the contrary, our views are supported by international guidelines and recommendations by scholars who are experts in the fields of genetics, ethics, philosophy, regulation of scientific interventions and children's rights.

Although we address only three points related to the editorial by Thaldar *et al.*, so as not to repeat the views we expressed in the Ramsay *et al. SAMJ* editorial,[2] this does not infer that we agree with their remaining points.

First, although it may appear proactive to develop guidelines that are 'future ready' and that uphold Constitutional values, whether HHGE is indeed part of our human future is still up for debate. To purport otherwise – or to point out that 'HHGE should be seriously considered' if it could, theoretically, help to address a public health crisis – may be an academically interesting exercise, but ignores fundamental realities of healthcare in SA and scientific advances globally. Arguing that 'future-ready' legislation could allow us to be ready to act when the technology is validated is therefore misguided, as the substantive ethicolegal concerns still require critical engagement.

Second, SA is part of a global community, and ignoring international guidelines and recommendations on HHGE or dismissing them because 'the WHO (World Health Organization) guidelines appear to be less directly applicable to the SA context, as they may not fully account for its unique realities and constitutional imperatives' both reflects a lack of understanding of the purpose of the guidelines, and ignores that they were drafted with the input of several South Africans.[3,4] Furthermore, it constitutes a failure to intellectually engage appropriately with the issues.

Third, in our editorial, we expressed concerns regarding the academic rigour of some of this group's work. Building on this critique, we now draw attention to the pervasive reliance on self-citation as a strategy to bolster their arguments, including in their response to our editorial. A more balanced approach requires substantive engagement with academic literature.

On 11 December 2024, the Southern African Society of Human Genetics hosted an Indaba titled 'Ethical, legal, and social implications of heritable human genome editing: A South African perspective'.[5,6] Over 115 participants, including genetic health professionals, genetic scientists, legal experts and ethicists, overwhelmingly expressed concern and dismay at both the tone and the substance of the approach of Thaldar *et al.* in the current debate over HHGE in the country. Importantly, National Health Research Ethics Council (NHREC) members present at the Indaba recognised the concerns raised, and committed to initiating the process for amending the section on HHGE in the *South African Ethics in Health Research Guidelines: Principles, Processes and Structures* (3rd ed.)[7] through a consultative process.

Our interpretation and views consider a broad range of factors on HHGE that have direct bearing on society at large, and that are echoed both by the local community and by international guidance.

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