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Joint Australian Academy of Health and Medical Sciences and Australian Academy of Science submission on the Assisted Reproductive Technology Guidelines

The Australian Academy of Health and Medical Sciences (AAHMS) and the Australian Academy of Science (AAS) welcome the opportunity to respond to the NHMRC Australian Health Ethics Committee limited review of the *Ethical guidelines on the use of Assisted Reproductive Technology in clinical practice and research (ART Guidelines)*. The AAS and AAHMS are Learned Academies that provide independent, authoritative, and influential scientific advice to government. We have amongst our Fellows some of Australia's leading experts in a range of scientific and health matters, including researchers, health professionals and individuals working in industry.

AAHMS and the AAS approached multiple experts for input to inform this submission. We have synthesised their contributions to each of the questions provided by the Australian Health Ethics Committee (AHEC) template below.

Consultation questions

10. Is the information in the introduction, abbreviations and key terms clear and accurate?*

- ☒ Yes, it is clear and accurate
- ☒ It is mostly clear and accurate (please provide comments below)
- ☐ No, the information is unclear and/or inaccurate (please provide suggestions for improvement below)
- ☐ No comment

There was some disagreement; experts were divided between the first and second options.

11. Specific comments on the introduction, abbreviations or key terms (250 words or less)

Experts commented there were several issues.

Introduction:

The term 'severe mitochondrial disease' is used twice, while the legislation uses 'serious'. We suggest maintaining consistency and avoiding the use of 'severe' to avoid confusion.

The Introduction repeatedly refers to mitochondria and to nuclear DNA, but does not mention mitochondrial DNA (mtDNA). While the procedure does indeed involve transfer of mitochondria rather than just mtDNA, the relevant form of mitochondrial disease is caused by changes/variants/mutations in mtDNA. It is suggested this is made explicit.

One expert commented that the meaning of 'particular risk' (p. 2) is unclear and suggested this be simplified to 'risk'.

Key terms:

Multiple experts commented there were issues with the definition of haplotype or haplogroup matching. One suggested greater clarity; another noted the high level of detail was inconsistent with the level of detail

provided about other terms in this table. Another noted the definition of haplotype or haplogroup is potentially misleading in its reference to the 2020 MDEWC report: 'A number of new studies (2020)…resulting from mitochondrial donation'. The studies themselves were reviewed in 2020 rather than being conducted in that year. This could be revised to 'Following the final approval of mitochondrial donation by the UK HFEA in 2016, a number of studies have examined aspects of mitochondrial-nuclear interactions resulting from mitochondrial donation'.

A point that could be added is that the background mitochondrial haplotype/haplogroup can influence the penetrance in some mitochondrial diseases such as Leber Hereditary optic neuropathy

The definition of reversion was described as incorrect or incomplete. As one expert described:

> 'The phenomenon of reversion was identified by studying human embryonic stem cells, in which some lines showed an increase in the level of carried over mtDNA relative to donor mtDNA during prolonged culture. These studies mostly involved two healthy mtDNA species so reversion can occur with healthy mtDNA and does not necessarily imply the phenomenon will cause mitochondrial disease. For that to happen, the level of heteroplasmy for the carried over mtDNA would need to rise above the threshold of a specific pathogenic mtDNA variant beyond which it causes cellular dysfunction. For most such variants this may require an increase to 70% or 95% of the total mtDNA or near-complete reversion to carried over mtDNA. We suggest the wording be changed to clarify that reversion is the phenomenon of carried over mtDNA increasing in amount, which could potentially result in mitochondrial disease if the extent of reversion was sufficient.'

Another expert commented that the guidelines could mention that reversion or carryover could occur in subsequent generations; the child produced may be at low risk of mitochondrial disease, but the offspring of the daughters could have a further increase in the level of mutant mtDNA.

The definition of 'carryover' is currently incorrect. It should read '…carryover arises when mitochondria are transferred from the mother's affected egg along with the cytoplasm containing the nuclear DNA'.

12. Are the guiding principles in the Supplementary Section (S4) clear and easy to understand?

- ☒ Yes, they are clear and accurate
- ☐ They are mostly clear and accurate (please provide comments below)
- ☐ No, the information is unclear (please provide suggestions for improvement below)
- ☐ No comment

13. Specific comments on the guiding principles (S4) in the Supplementary Section (250 words or less)

One expert noted that although there have been great strides in the development of the Assisted Reproductive Technology (ART) that would need to be deployed for mitochondrial donation, the techniques are by no means totally refined, and they believed there are still major procedural questions that will need to be addressed. The guiding principles outlined in section S4 are well constructed, and it is imperative that they be followed.

14. Is the guidance on information giving and counselling (S5) clear and easy to understand?

- ☒ Yes, it is clear
- ☒ It is mostly clear (please provide suggestions for improvement below)
- ☐ No, the information is unclear (please provide comments below)
- ☐ No comment

There was some disagreement; experts were divided between the first and second options.

15. ***Specific comments on information giving and counselling (S5) in the Supplementary Section (250 words or less)***

The major comment related to this section is that the requirements around consent and understanding of the various steps involved in mitochondrial donation could be more sensitively presented and described. For example, people who are considering participating in mitochondrial donation research may have already had extensive genetic counselling. The draft document can be interpreted such that all potential participants will be required to undergo rounds of genetic and fertility counselling. It would be helpful for existing knowledge and/or experience to be acknowledged. Further, the requirement should be revised such that it is an assessment of existing knowledge, with additional information to be provided where required.

S5.1.3 is endorsed for its emphasis on sensitivity—which highlights the need for sensitivity to be more firmly reflected throughout this section.

Additionally, mitochondrial genetics is highly complex, so the counselling services that need to be provided must include involvement from clinical genetics teams with expertise in mitochondrial genetics (including clinical geneticists and genetic counsellors).

Structurally, sections 5.2.2 and 5.2.3 could be restructured to separate the information and consent requirements for egg donors relevant to mitochondrial donation from that required for the prospective (and her partner if she has one). This should reflect that informed egg donors for mitochondrial donation may not require the same depth of understanding of mitochondrial disease and the implications of mitochondrial donation as the prospective mother, research participant or spouse. Whilst all parties should be informed, delineation about what needs to be provided for the consent of egg donors for mitochondrial donation beyond the considerations already covered elsewhere in the ART guidelines in relation to ART egg donation should be articulated.

One expert commented that while these guidelines are most likely discussing 'egg donors', it should be noted that other types of donors can be part of ART. For instance, a prospective mother participating in mitochondrial donation may access donor sperm to overcome male factor infertility or in the absence of a partner. The term 'donor' could be further clarified to enhance the interpretation and usability.

Multiple experts suggested that S5.1.2 be clarified. This should include clarification that the appreciation of risks should relate to both the trial participant/patient and any offspring. Additionally, the second dot point could be restructured, such that the point flows: women's health might be complicated by her mitochondrial disease, leading to negative impacts on ART treatment and pregnancy.

Section 5.2.2 refers to 'the possibility of reversion and carry-over of mitochondria'. This should be reordered to reflect the order of occurrence: 'the possibility of carryover and reversion of mitochondria'.

16. ***Is the guidance on information consent (S6) clear and easy to understand?***

- ☒ Yes, it is clear
- ☐ It is mostly clear (please provide suggestions for improvement below)
- ☐ No, the information is unclear (please provide comments below)
- ☐ No comment

17. ***Specific comments on consent (S6) in the Supplementary Section (250 words or less)***

There were no specific comments in relation to this section.

18. ***Is the guidance on the use of donated gametes (S7) and responsibility for stored gametes and embryos (S8) clear and easy to understand?***

☒ Yes, it is clear

☐ It is mostly clear (please provide suggestions for improvement below)

☐ No, the information is unclear (please provide comments below)

☐ No comment

19. ***Specific comments on the use of donated gametes (S7) and responsibility for stored gametes and embryos (S8) in the Supplementary Section (250 words or less)***

The guidance appears appropriate for both.

20. ***Is the guidance on record keeping and data recording (S9) clear and easy to understand?***

☒ Yes, it is clear

☐ It is mostly clear (please provide suggestions for improvement below)

☐ No, the information is unclear (please provide comments below)

☐ No comment

21. ***Specific comments on record keeping and data recording (S9) in the Supplementary Section (250 words or less)***

Accurate and complete record keeping is essential for any clinical trial, particularly where new technologies are under consideration. It should be noted that no outcome data has been forthcoming from mitochondrial donation providers from the United Kingdom. This has generated a degree of mistrust in some parts of the community and some political circles. It is critical for structures to be put in place that would enable reporting of the outcomes of the Australian clinical trial, while appropriately protecting the privacy and anonymity of study participants.

22. ***Is the guidance on sex selection in mitochondrial donation (S10) clear and easy to understand?***

☒ Yes, it is clear

☐ It is mostly clear (please provide suggestions for improvement below)

☒ No, the information is unclear (please provide comments below)

☐ No comment

23. ***Specific comments on sex selection in mitochondrial donation (S10) in the Supplementary Section (250 words or less)***

Experts consulted by the Academies were divided on this section. One felt that while it was clear, it was problematic in that it contained insufficient information. This might be addressed by drawing further upon the full *Ethical Guidelines on the use of Assisted Reproductive Technology in clinical practice and research*. It might also benefit from discussion of counselling given the potential concerns from prospective parents.

One expert strongly endorsed the statement that sex selection of embryos is not necessary, as it would greatly reduce the number of embryos for implantation in what is already a complex procedure.

Another expert commented this section seemed to conflict with the 8.13 and 8.14 statements from the 2017 ART guidelines, and questioned whether resolving this might require legislative change:

Sex selection techniques may be used to reduce the risk of transmission of a genetic condition, disease or abnormality that would severely limit the quality of life of the person who would be born, when there is evidence to support:

• claims that the condition, disease or abnormality affects one sex significantly more than the other (see paragraph 8.16)

• that the risk of transmission is greater than the general risk of the condition, disease or abnormality occurring within the general population.

This expert noted that if mitochondrial donation techniques are unable to absolutely prevent carryover of the mutant mtDNA, then there may be risk (albeit reduced) to the child. However, in the case of Leber Hereditary Optic Neuropathy, and as has occurred in at least one IVF instance, the parents may choose a daughter to reduce the risk of a son—who, without mitochondrial donation, would have a significantly greater risk of vision loss than a daughter. In this instance, the flipside is the potential for ongoing transmission from a daughter. A parent wanting to guarantee their grandchildren are not at risk should select a son—while a son would have a higher personal risk, there is zero chance of passing this on to any of his offspring.

24. Do you have any other comments in relation to the Supplementary Section? (500 words or less)

Multiple experts commented that if this document is written for an average person to understand, it is too complex. This may be addressed by commissioning a formal 'plain English' review or similar.

There is some inconsistent terminology used throughout the guidelines. For example, the guidelines use the terms 'mother', 'prospective mother' and 'intending mother'. The term 'prospective mother' should instead be used consistently.

In case it is helpful, we provide further explanation of the issues around carryover, reversion and potential that we commented on in relation to Key Terms. There are really three distinct concepts here.

The first, carryover, may be defined correctly with the amendments suggested in Question 11 and corresponds to the process whereby in an egg or zygote generated by mitochondrial donation, a small proportion of mtDNA is derived from the egg or zygote from the patient (mother) while the majority comes from the donor. This carryover is the starting point for the mtDNA present in the zygote and early embryo in the days following the ART procedure, and the developers of these procedures have typically aimed for carryover to represent no more than 2% of total mitochondrial DNA in the zygote.

The second concept, reversion, is the process whereby carried over mtDNA from the patient (mother) can potentially increase in amount relative to the donor mtDNA during embryogenesis, or in prolonged culture of embryonic stem cell lines. Reversion can be partial, where the carried over mtDNA increases to say 30% or 70% of the total mtDNA or potentially complete where it increases to 100%. Reversion, per se, does not cause mitochondrial disease and can occur with two healthy mtDNA genomes or when the mtDNA from the patient (mother) carries a disease-causing variant.

The third concept is the potential risk of reversion resulting in mitochondrial disease, which requires understanding of mtDNA heteroplasmy and the mtDNA threshold effect. mtDNA variants that underlie serious mitochondrial disease are known as pathogenic mtDNA variants. Human cells contain thousands of mtDNA molecules and when these have an identical sequence it is called homoplasmy. When some mtDNA sequences within the cell differ, it is known as heteroplasmy and the level of heteroplasmy can potentially range from 1% to 99% of cellular mtDNA. Pathogenic mtDNA variants only cause mitochondrial disease when they exceed a threshold level above which there is insufficient healthy mtDNA for normal cellular function. For most pathogenic mtDNA variants, the threshold level of heteroplasmy is in the range of 70% to 95%.

In the context of mitochondrial donation, carryover is typically of the order of 2%, so the extent of reversion would need to be very high for carried over mtDNA containing a pathogenic variant to rise to a level of say 70% to 95% heteroplasmy in order to cause disease.

This briefing has been informed by contributions from Fellows of the Australian Academy of Science and the Australian Academy of Health and Medical Sciences. We are grateful for their valuable contributions.

For questions about this submission, or to arrange a consultation with Fellows of the Academies, please contact Lanika Mylvaganam (lanika.mylvaganam@aahms.org) at Australian Academy of Health and Medical Sciences or Chris Anderson (chris.anderson@science.org.au) at the Australian Academy of Science.