Voices of experience in periviable decision-making and artificial placenta technology

Boer, A.H.A. de

Chapter 9

The ethical concerns of Dutch perinatal healthcare professionals and experienced parents regarding artificial amnion and placenta technology

Angret de Boer, Dominic Wilkinson, Rania Kalaai, Marieke de Vries, Marije Hogeveen, Sylvia A. Obermann-Borst, Marijn J.J. Vermeulen, Juliette S. van Haren, Peter Andriessen, Martine C. de Vries, André Krom Rosa Geurtzen*, E.J.T. (Joanne) Verweij*

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Abstract

There is ongoing research into so-called artificial amnion and placenta technology (AAPT); the hope is to support extremely premature infants by mimicking the in utero environment, potentially reducing mortality and morbidity compared to conventional care. While implementation into clinical care is still some way ahead, this study seeks to understand the key ethical concerns of parents and healthcare professionals (HCPs), crucial for guiding the responsible development and application of this technology. To address these concerns, eight focus-group interviews and five individual interviews were conducted with 46 healthcare professionals working in perinatal care and 15 parents who experienced an actual or imminent extremely premature birth. The interviews were recorded and transcribed verbatim. The transcripts were thematically analysed and revealed key concerns, represented by the following five themes: (1) a slippery slope, focusing on the impact of AAPT on viability, (2) human nature and unnaturalness, (3) risks and benefits for infant, mother and beyond, (4) replaceability of the mother, and (5) resource allocation, inequality, and inequity. Dutch parents and HCPs expressed a range of viewpoints regarding the implementation of AAPT, ranging from opposition to cautious optimism. Addressing these concerns and integrating stakeholder perspectives is essential for guiding responsible policy-making for this emerging technology, and could also impact its acceptance.

Introduction

In recent decades, several research groups around the world have been engaged in research on the development of a system that mimics the function of the amniotic sac, amniotic fluid and placenta: the artificial amnion and placenta technology (AAPT), also sometimes referred to as ectogestation, or partial ectogenesis.[1-3] AAPT would potentially be able to provide support for infants born extremely prematurely, in a way that is more similar to the in utero environment (retaining fetal circulation), and with less mortality and morbidity than conventional intensive care support.[1,3,4] Animal studies show promising results, and there is the potential for first in-human trials in the near future.[5-7] Such trials are essential to determine whether the AAPT would be safe and effective in extremely premature newborns.

Although the AAPT is still far from implementation into clinical care, we believe it is important to start thinking about the implications of its clinical use.[8] There is a growing body of literature identifying a variety of ethical issues and implications of the AAPT.[9-13] Pressing issues for clinical translation include informed consent for novel and experimental technologies and equity of access to the technology.[14] However, there is no literature on which ethical issues are of most concern to stakeholders. This study aims to contribute to filling this gap by obtaining insight into the primary ethical concerns of parents who have experienced a threatened or actual extremely premature birth and of healthcare professionals (HCPs) involved in perinatal care for extremely premature infants. Exploring these ethical concerns will help with critically reflecting on the development of this technology.

Methods

TINY-study and study design

This article is part of the Dutch research initiative "Toward INdividualized care for the Youngest" (TINY-study).[15-18] The TINY-3 study focusses on the ethical concerns and considerations surrounding the potential use of the AAPT as a new treatment for extremely premature infants.

Figure 1 illustrates the methodological framework of the TINY-3 study, which consisted of different phases (*Supplemental files TINY-3, file 2)*. The initial phase involved a stakeholder meeting using the Guidance ethics approach (*Intermezzo C*).[19] After this, phase 2 consisted of focus group discussions and individual interviews to deepen the analysis of the ethical issues highlighted during the stakeholder meeting. The study's findings are presented across four interconnected articles. The other articles explore the crucial considerations that must be addressed before moving forward with AAPT trials and focus on the counselling and informed consent process.[20,21] This article extends that work, focusing specifically on the most urgent ethical concerns and considerations of the AAPT after implementation into clinical care, as identified by participants.

Selection of participants

Participants for this study were recruited through various channels as described in *Supplemental material TINY-3 file 1*. Eligible participants were HCPs involved in perinatal care or parents who experienced an actual or imminent extremely premature birth (before 28 weeks gestation).

Data collection and analysis

A comprehensive interview guide was developed (*Supplemental material TINY-3 file 3*), informed by both the stakeholder meeting and the expertise of the multidisciplinary research team. Two to three members of the research team moderated the interviews, which were recorded and transcribed verbatim. Analysis of the transcripts followed thematic content analysis as described by Braun and Clarke, using both deductive and inductive coding.[22] The coding was independently performed by researchers AB and RK. The results are supported by quotes that were translated from Dutch to English by the authors.

Results

We conducted six focus group interviews with HCPs (n=46), and two focus group interviews (n=13) and five individual interviews with experienced parents. The HCPs represented various specialties, and parents had different experiences with extremely premature birth. Demographic information is presented in *Table 1A and 1B (Supplemental files TINY-3, file 4).*

Themes that emerged from the data focus on ethical concerns and considerations relating to the potential future use in standard care with AAPT, namely: 1) slippery slope, 2) human nature and unnaturalness, 3) risks and benefits, 4) replaceability of a mother, and 5) resource allocation, equality and equity. Parents expressed mixed views on the development of AAPT, generally leaning towards optimism. HCPs exhibited more scepticism, ranging from outright opposition to the development of AAPT among some professionals, through to others who recognized the potential of the technology, albeit with significant concerns.

Slippery slope

A great concern of both parents and HCPs was a 'slippery slope', suggesting that the development of the AAPT will lead to a chain of consequences. During the interviews, participants asked the following questions: "*How far are we willing to go?", "What is the limit?", "How early do we want to resuscitate children?"*, or *"What is still acceptable?"*. The HCPs and parents argued that with the development of AAPT, the limit of viability would likely go down. The HCPs were anxious that it would ultimately lead to full ectogenesis.

Human nature and unnaturalness

The interviews revealed a strong sentiment among HCPs and parents regarding the overstepping of natural boundaries (in Dutch *"Maakbaarheid van de wereld").* HCPs emphasized how artificial and mechanical the world has become. In this context, one HCP reflected on

extremely premature birth: "*The question is: is this normal? In nature, a baby animal will not survive extremely premature birth. We are the only species that live because we think we have the right to do so*." The perception of the world as increasingly unnatural was a source of concern, as some felt that there is no point of return with the development of AAPT, which is also an example of the previous theme 'slippery slope'. As a HCP stated: "*If you say yes to this, it only gets more artificial*", while other HCPs recognised the overlap with current practice asking: "*What makes this so different from treating 24-weekers*?".

HCPs and parents discussed the tension between keeping infants alive and recognizing the limits of interventions and technology. As one HCP noted: "*As people, and especially as HCPs, we tend to fix things*." Parents echoed these concerns, with one parent reflecting, "*Sometimes we go a bit too far*" and another admitting "*I find it complicated to knowingly keep children alive [just] for the sake of keeping them alive*". The participants had concerns about over-intervention, with both groups asking how far society should go in shaping human life through technological means. One parent stated: "*With the experience I have now, I think we should let nature take its course*." HCPs acknowledged that death is a natural part of life, as one parent pointed out: "*It is also okay to die at some point*".

In contrast, several parents and HCPs noted that while this technology may initially feel very unnatural and overstepping natural boundaries, it is ultimately attempting to replicate something inherently natural. As one HCP asked the group: "*Is this really artificial, or do we just call it artificial because it's different from the current way we do things?"* HCPs, in particular, compared it with the fact that current care practices are themselves also unnatural.

Risks and benefits

The potential for an increased number of iatrogenic premature births in the context of AAPT was a concern especially among HCPs, as it appears that a caesarean section might be required to transfer the baby to the AAPT-device. They worried that the necessity to perform a caesarean section could lead to more frequent, possibly unnecessary, premature deliveries. One HCP remarked: "*You're subjecting the mother to a caesarean and potentially taking the baby out too early*". The HCPs were apprehensive that the presence of AAPT might prompt earlier interventions in cases where waiting longer might be considered safe under current care practices. As a result, HCPs mentioned that infants who otherwise would have remained in utero longer might instead be delivered by caesarean in the context of AAPT, which "*could cause more harm than it solves*". One HCP asked, "*Is a caesarean really necessary? I still don't see the benefit over a vaginal birth*."

Parents and HCPs discussed the weighing of the uncertainty of outcomes against possible risks and negative consequences, such as impacts on parent-child bonding. Some parents indicated that if such technologies could prevent specific complications, they would find the possible risk and negative consequences of AAPT worthwhile. However, others questioned whether the risks associated with interventions needed in the context of AAPT,

like performing a caesarean section at an extremely early gestational age, were justified given the uncertain outcomes.

Replaceability of a mother

Both parents and HCPs discussed the idea of the mother's replaceability by AAPT. Some HCPs expressed concerns about how this would impact the often existing guilt of the mother, with one HCP stating, "*[Mothers] may think the machine is better than their own body*", suggesting that the mothers may perceive the technological interventions as more reliable or efficient.

Parents discussed that technology may negatively alter the maternal experience of the pregnancy, including the bonding with the child. They also emphasized that technological replacement may "*take away how special a pregnancy is*" and detach mothers from their natural connection with their babies during pregnancy.

HCPs expressed scepticism about the possibility of replacing the natural process, describing it as "*arrogance to think you can mimic a normal pregnancy*". They highlighted the complexity of the interaction between mother, child, and placenta, stating: "*That is so subtle, dynamic... I cannot imagine that you can mimic this so specifically without impacting future illnesses*."

Resource allocation, inequality, inequity

HCPs argued that AAPT may not be a desirable development because of the costs that will be involved. They wondered whether the costs of this high-tech treatment outweigh the benefits. The money could also be invested differently, as one HCP suggested: "*Perhaps a fraction [of what is spent on this technology] could also be allocated to improving the care of current 24-week preterm infants. I believe that step should come first".* It was noted that poverty is widespread, and healthcare is already very expensive. With this development, costs are expected to rise further, potentially leaving even more people unable to afford healthcare. This may lead to AAPT being a treatment for the rich people in certain parts of the world.

Furthermore, parents added that this money may be better spent on alleviating or preventing the burden for people who are already struggling in life. HCPs mentioned the fact that there is no budget to extend the follow-up care for individuals that are born extremely prematurely and found it incomprehensible that all this money would be spent on this development instead of on the follow-up first.

With selecting a particular group as research population (i.e., those currently at the borderline of viability), parents worried about the exclusion of other groups of extremely premature infants: "*So, there are also children born at 24, 25, or 26 weeks who simply cannot participate because [certain circumstances would make them] not eligible, right?".* The HCPs were particularly concerned about the exclusion of infants based on the allocation of re-

sources. For example, if the care with AAPT would be centralized in one centre, a baby would be excluded when born in another centre. This would be unfair according to them.

Proportionality emerged as a significant ethical concern of the participants, which was also linked to issues of inequity. Both parents and HCPs questioned whether the drive to improve care and further develop technologies is justified considering potential financial, logistical, and personal implications for society, healthcare systems, the infants and their families. Concerns were raised about the substantial financial and human resources invested in these technologies, which could arguably better be allocated to addressing other pressing societal needs, such as poverty reduction and shortages. As one HCP noted, "*You have to train people [...] There's already a huge shortage [of personal in healthcare] —where will we find these people*?"

Furthermore, several HCPs highlighted concerns about global health equity, feeling it is disproportional to focus on high-cost technological advancements in some regions while basic healthcare infrastructure remains underdeveloped in other parts of the world.

Discussion

Although there has been considerable discussion of the ethics of AAPT, this is the first study to explore in detail the perspectives of parents who have faced (imminent) extremely premature birth and of HCPs working in perinatal care who might be expected to use this technology. Overall, participants' views on the desirability of the development of an AAPT varied from being against this new technology to acknowledging the potential of this technology, although with significant concerns. Concerns that emerged from interviews included the potential impact on (the limit of) 'viability', the risk of overstepping natural limits, the balance of risks and benefits, and issues related to resource allocation, equity, and access to care.

Viability

One of the key concerns among HCPs was the potential impact of AAPT on the threshold of viability for extremely premature infants (i.e. the earliest gestational age at which premature infants can potentially be saved). This concern may be linked to the relatively conservative nature of current Dutch views on medical care at extremely preterm gestational age.[23] Previous studies have observed that Dutch professionals tend towards maintaining the current threshold of 24 weeks due to the perceived lack of good outcomes.[17,18,24] Concerns about this technology may overlap with a more general suspicion of the use of advanced medical techniques to save increasingly premature infants and the implications of saving those infants. If the threshold of viability were shifted, this may have implications both for neonatal care (i.e., whether it would be permissible to withhold survival focused care at parental request), and for obstetric care (i.e., whether abortion would be permissible at a certain gestational age).[25]

Our findings are in line with a previous quantitative survey of Australian HCPs. This study revealed that professionals anticipated that AAPT would shift the limit of viability. However, they expressed ambivalence about this potential change and whether the adoption of AAPT should become standard practice.[26]

However, is the concern about viability realistic? One of the leading research groups in AAPT has emphasized that their aim is not to alter the limit of viability.[2] They imply that it would be used to improve outcomes for infants who currently receive conventional support. Nevertheless, it seems plausible that, if successfully translated to humans, AAPT could enable the survival of extremely premature infants who could not previously have been saved. This may apply even if it would not intentionally be used to alter the limit of viability. For example, if AAPT demonstrates efficacy for infants born at 22 weeks in a country where infants at this gestational age are regularly treated, that may have implications for countries like the Netherlands, with a more conservative viability limit of 24 weeks. Consequently, the introduction of AAPT could challenge established ethical, medical, and societal standards.

It is essential to establish clear policies and ensure that any adjustments to viability thresholds are carefully considered before AAPT is implemented in clinical care. It may be important to clarify the relationship between neonatal treatment and thresholds for access to abortion.[27] However, it is not clear that concerns about the limit of viability are strong reasons to avoid pursuing AAPT. For one thing, there are strong practical, biological and medical constraints that entail that at least in the short-medium term, the technology is highly unlikely to dramatically alter the limit of viability (i.e. save infants much earlier than the current physiological limits).[26] Secondly, the mere fact that the technology would make it possible to save more premature infants would not in itself provide a reason not to pursue it. Advances in neonatal intensive care in the last five decades have shifted the borderline of viability from 28 to 22/23 weeks. But that fact in itself does not give reason to regret such advances.[26]

Natural limits

Secondly, concerns about AAPT overstepping natural limits echo broader Dutch societal fears of disruptive medical technologies, often framed as "playing God". Related to this is also a diminishing resilience and societal acceptance of the things that remain 'out of our control'. Similar concerns from Dutch stakeholders have been documented in discussions about CRISPR, where the ability to edit genes is viewed by some as crossing ethical boundaries due to its profound implications on human life and the natural order.[28] Reproductive genetic technologies, such as in vitro fertilization and embryo selection, have likewise faced initial resistance rooted in fears of tampering with human natural reproductive processes, although societal acceptance has grown as these methods proved their utility and safety.[29-31] A historical parallel can also be drawn with organ transplantation, which was initially perceived as unnatural and morally contentious before becoming a routine and life-saving intervention.[32] Moral concerns in this debate were solved by improving treat-

ment and outcomes through technological innovation.[32] These examples suggest that while initial resistance to the AAPT may reflect values about the sanctity of natural processes, acceptance may increase as the technology demonstrates tangible benefits and aligns with ethical safeguards. Addressing these concerns and integrating stakeholder perspectives is essential for guiding responsible policy-making for this emerging technology, and could also impact its acceptance.

Risks and benefits

Thirdly, participants were concerned about the uncertainty associated with the health benefit balanced against risks of this technological development. The potential benefits for the infant could be substantial, though they remain uncertain at this stage, while potential harms include iatrogenic extremely premature birth, the burden on the mother and potential negative consequences for the infant, the parents, the family and society. This theme reflects broader concerns in the literature about the balance between potential benefits of perinatal technologies and the risks for both the infant and the mother.[33]

One challenge, particularly in the early stages of developing this sort of technology, is the profound uncertainty surrounding its risks and benefits. This ambiguity complicates ethical decision making regarding the appropriate timing for offering the therapy. Once there is some accumulated experience, a different issue is that risks and benefits may be distributed unevenly. As with fetal therapies or fetal surgery, AAPT does not offer direct medical benefits for the pregnant person and may introduce significant medical risks. How should risks to the mother be weighed against benefits to the foetus/infant? If there would be an evident negative risk-benefit balance for mother and infant together, it may not be ethical to offer treatment. However, if the risks are more finely balanced - where the benefits to the foetus/infant may outweigh the risk for the mother and infant, then the decision ultimately comes down to the informed consent of the mother through shared decision making, as this would make it a preference-sensitive choice. This process must involve thorough discussions about values of all parties involved, the risks she is willing to accept for herself and for her infant, and the potential benefits for the infant.

Resources

Lastly, reasonable use of resources was a key concern for both parents and HCPs, particularly regarding the investment of funds and personnel in the development of AAPT. Stakeholder concerns reflect broader challenges in healthcare resource allocation, where the balance between innovation and equity must be carefully navigated. A method to evaluate and allocate societal investment could involve cost-effectiveness analyses, which often require statements on the monetary value of human life. For AAPT, such an analysis would need to compare the cost-effectiveness of standard neonatal intensive care unit (NICU) treatments and AAPT. Whether this technique is cost-effective will depend on how much it costs, and also on its incremental benefit. One critical consideration for AAPT is the value placed on saving the life of extremely premature infants around or even prior to

the current limit of viability.[34,35] On usual analysis, conventional forms of NICU, even for the most premature infants, are highly cost-effective because they typically yield many years of life, and the majority of survivors are not severely impaired, resulting in a high amount of quality-adjusted life years.[36] However, some of the HCPs and parents questioned whether resources should be spent on saving the lives of these premature infants. This might indicate that decisions about who to treat are connected to broader questions and dilemmas about resource allocation, moral status and social value placed on very immature lives. Such dilemmas inevitably involve determining who should be included or excluded, which in turn raises the critical question of how such decisions can be justified. One study found that the life of a premature infant was valued less than that of older children, such as a two-month-old or a seven-year-old, reflecting both the uncertainty of outcomes of an extremely premature infant and societal attitudes toward this group.[37] It is conceivable that some societies might choose not to invest in AAPT or related technologies because they place greater value on healthcare for older individuals. However, this would be controversial, and conflict with approaches that emphasise the intrinsic worth of all lives and the unique vulnerabilities of extremely preterm infants.

A different concern, expressed in particular by the HCPs in this study was that the development and implementation of AAPT would exacerbate global health inequalities, as its advanced capabilities would likely be concentrated in high-income countries, where resources for NICUs are already well-established. In low- and middle-income countries (LMICs), where NICUs are scarce or poorly equipped, access to such cutting-edge technologies would remain out of reach for the majority.[38] This disparity mirrors existing inequities in neonatal care, where infants in LMICs already face significantly higher mortality rates due to the lack of advanced interventions.[39] However, these concerns are not necessarily sufficient ground to halt the development of AAPT. Such concerns could be addressed by prioritizing strategies that promote equitable distribution and support for NICU-infrastructure development in LMICs. To a certain extent it then becomes an empirical question whether that can be combined with further developing the AAPT (depending on, for instance, where the funds needed to prioritize strategies to promote equitable distribution need to come from).

Strengths and limitations

This study is among the first to qualitatively explore HCP' and parents' ethical concerns on care with AAPT. A diverse group of participants was interviewed, enriching the variety of perspectives. Additionally, the multidisciplinary approach of the research team strengthens the study's credibility.

However, the study also has some limitations. First, results are dependent on personal moral perspectives of the participants and the results must be interpreted against the sociocultural background of the Netherlands and the physicians' professional field. However, in the context of other technologies and in other countries, certain ethical concerns

which arose during these interviews, such as overstepping natural boundaries, allocation of resources, equality and equity, are also very relevant concerns. Whether these stakeholder concerns can be generalized to other countries remains to be determined. Second, while participants from obstetrics were purposefully included, most HCP participants had backgrounds in neonatology, potentially narrowing the range of professional insights. Another possible limitation is selection bias, as individuals with strong positive or negative opinions about AAPT may have been more inclined to participate. However, thematic saturation was achieved, and the results neither unequivocally support nor oppose AAPT.

Conclusion

Exploring the perspectives of relevant Dutch stakeholders allowed us to identify key ethical concerns and considerations surrounding the potential implementation of the AAPT. Recognizing these concerns is essential to understanding the underlying values and normative dimensions that will shape its acceptance and impact. While these concerns are critical in order to minimize potential negative ethical and societal implications, they may not provide reasons to slow down the development of AAPT. Equally important is the uncertainty regarding how individuals in the perinatal care field—both those who deliver high-tech care and those who have received it—perceive this technology. Perspectives of these stakeholders ranged from ethical opposition to cautious optimism about its potential. By acknowledging and integrating these diverse viewpoints into the development process, we can foster a balanced and inclusive approach that respects stakeholder values in advancing or halting further technological developments. These findings can provide a foundation for formulating policies and guiding further discussions to ensure that the potential further development and implementation of AAPT happens responsibly and equitably.

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Supplemental files TINY-3 study (chapter 7-9)

- File 1: Detailed description of the methods
- File 2: Figure 1: Different phases of the TINY-3 study
- File 3: Interview guide TINY-3
- File 4: Tables demographic information participants

Supplemental file TINY-3 study, file 1 (Detailed description of the methods)

TINY-study & study design

This research is part of the Dutch study called Toward INdividualized care for the Youngest (TINY), initiated by three perinatal centers in the Netherlands: Erasmus MC Rotterdam, LUMC Leiden, and Radboudumc Nijmegen. While TINY-1 and TINY-2 studies focused on periviability guidelines, personalization, and parental values in decision-making surrounding extreme premature birth, TINY-3 focuses on the artificial amnion and placenta technology (AAPT) in extreme prematurity.[1-4]

As part of the TINY-3 study, a stakeholders meeting was performed following a guidance ethics approach.[5] This approach is not primarily focused on the question whether a technology is acceptable or not, but rather starts with the question how a technology can be given a responsible place in society. In the meeting, we discussed the actors who could be affected by the implementation of AAPT (and therefore should have a say in how and under what conditions the technology should be developed and used), the potential positive and negative effects that introduction of the AAPT could have and which values would be at stake with these effects.[5] Lastly, participants developed possible strategies to ensure the responsible development and use of the technology, specifically distinguishing options to promote key values by changes in the technology itself, options in the specific context in which the technology could be employed (e.g., organizational changes or agreements needed to promote key values) and options concerning what users of the AAPT themselves can do to promote responsible use.[5] With the input of this stakeholder's meeting, we performed focus group interviews and individual interviews to further explore and deepen the main findings of the stakeholders meeting:

I. Conditions and considerations regarding the human AAPT trials;
II. Considerations and concerns regarding the informed consent procedure during counselling and decision-making about the human AAPT-trials;
III. Ethical concerns regarding the care with the AAPT, such as inequality or slippery slope;
IV. The AAPT design, as potential solution for some of the unwanted effects of the AAPT.

This article presents the TINY-3 results on conditions for the first in human trials of the AAPT. The Scientific Committee of the Leiden University Medical Centre assessed the study protocol and waived the need for ethical review (reference: 23-3052).

Study participants

Participants were recruited through the TINY-database which consists of parents who experienced an (imminent) extremely premature birth and the Dutch patient association Care4Neo, social media (e.g., LinkedIn) and the researchers' networks. Inclusion criteria for this study were (1) working as HCP in perinatal care, or (2) being a parent who experienced an extremely premature birth before a gestational age of 28 weeks.

TINY-database

The TINY-database was created using Castor to include parents who experienced an imminent or actual extremely premature birth and were interested in participating in neonatology research.[1,4] Recruitment for the database was conducted through various channels, including the Dutch patient organization Care4Neo, the Dutch platform Stille Levens - kenniscentrum Babysterfte, physician networks, social media platforms associated with participating hospitals and researchers, and by contacting parents who had consented to further communication from prior studies (PreCo study - Prenatale Counselling in extreme prematurity, CODA study)[6,7].

To be included in the database, participants needed to meet one of the following criteria: (a) had an extremely premature birth between 23 and 26 weeks gestational age (GA) after 2010, or (b) experienced an imminent extremely premature birth between 23 and 26 weeks GA after 2010, but delivered at a later GA. Upon providing informed consent for inclusion in the database, all parents were asked to complete a brief online questionnaire. This questionnaire gathered demographic information about their experience with extremely premature birth (e.g., decision-making regarding intensive care or palliative comfort care, GA at imminent birth, GA at actual birth, and survival of the child) as well as their personal background (e.g., age, educational level, and native language).

Data collection

Focus group and individual interviews were conducted by members of the research team with various backgrounds (PhD-student, neonatologist, maternal-fetal-medicine specialist, ethicist, psychologist). The participants all granted informed consent before starting the focus group interviews.

An interview guide was developed based on the previously performed stakeholders meeting and the expertise of our multidisciplinary team. It comprised (I) general instructions about the technique and (II) open-ended questions corresponding to the themes that were found in the stakeholders meeting. It was emphasized that the discussion should focus on the current status of the development and the most urgent topic: the potential upcoming AAPT trial, rather than on possible applications of implementation in clinical care. During the interviews, prototypes developed by the PLS consortium were present to provide participants a clearer, more concrete understanding of what the technology could look like.

Data analysis

Results were analysed and coded independently by two authors (AB, RK) in Atlas.ti, using thematic content analysis following Braun and Clarke's guidelines.[8] This process included becoming familiar with the data, generating initial codes to develop a codebook, identifying patterns and themes within the data, reviewing and updating codes and codebook, and defining and naming the themes. The codebook and analysis were discussed within the team and adjusted in multiple rounds until agreement was reached.

Manuscripts TINY-3

The data collected from the interviews was extensive and multi-faceted, addressing various ethical considerations regarding the AAPT and the upcoming human trials. To thoroughly analyse and present these findings, we divided the data into four distinct manuscripts, each corresponding to key themes outlined in the interview guide and additional themes that emerged during our analysis.

Given the volume and complexity of the data, as well as the ethical implications raised throughout the discussions, four critical topic are separated into 4 manuscripts (see also *figure 1*) allowing for thorough examination of each critical theme. This approach ensures that fundamental ethical questions and concerns identified during the interviews receive the necessary attention and discussion.

The first paper focuses on the conditions surrounding the initiation of first-in-human trials.

References

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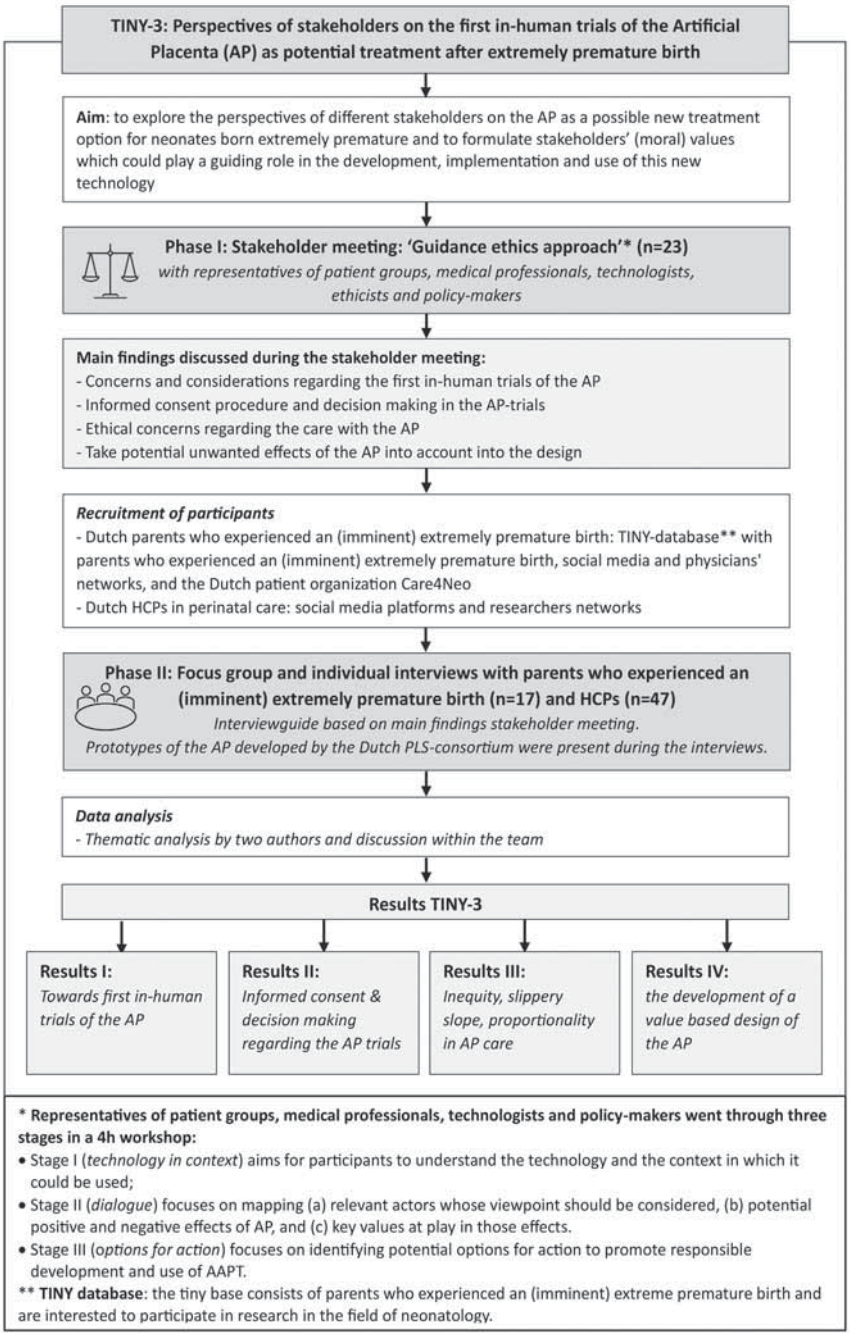
Supplemental file TINY-3 study, file 2 (Figure 1)

Figure 1 Different phases of the TINY-3 study



Supplemental file TINY-3 study, file 3 (Interview guide tiny-3 (translated from dutch to english)

Introduction:

- Explanation about how the focus group interviews will be performed, some regulations and practical matters
- Informed consent and demographic information
- Introduction to the topic: treatment of extreme prematurity and the current status of the development of the artificial amnion and placenta technology, which is the study phase before the first-in-human trials might start (i.e., before the first baby is placed in the artificial amnion and placenta technology). It can/may still be decided that this is not desirable.

1. ***Ethical Considerations for the Application of the Artificial amnion and placenta technology:***
    - Is the development of the artificial amnion and placenta technology a desirable advancement? Why or why not?
    - What are your primary ethical dilemmas associated with the application of the artificial amnion and placenta technology in humans? Why?
    - What ethical conditions must be met before first in human trials with the artificial amnion and placenta technology could be started?
        - What actions are necessary to fulfill these conditions?
2. ***Counseling and Decision-Making at the Individual Level***
    - Interview with parents:
        - What personal arguments, reasons, or circumstances might influence your decision to participate or not participate in such a trial?
        - What support or information would you need to make an informed decision about participating in the study involving the application of the artificial amnion and placenta technology in humans?
    - Interview with Healthcare Professionals:
        - What minimum standards do you believe counseling should meet to enable parents to make a decision about participating in the first study involving the application of the artificial amnion and placenta technology in humans?
3. ***Design of the Artificial amnion and placenta technology:***
    - Which aspects of current daily care for infants between 24-28 weeks of gestation in the NICU do you consider essential to retain in an artificial amnion and placenta technology?
    - What negative aspects of the current daily care for infants between 24-28 weeks in the NICU does the artificial amnion and placenta technology have the potential to improve or resolve?
    - What minimum conditions must the design meet before we can further develop or utilize the artificial amnion and placenta technology?

Present physical and digital prototypes.

- Do you still agree with the conditions you previously mentioned, or do you have any additions?

Supplemental file TINY-3 study, file 4 (Tables: demographic information participants)

Table 1A Demographic information of the healthcare professionals

Healthcare professionals	N=46
Specialty	
NICU nurse	16
Neonatologist	12
Nurse practitioner NICU	5
Maternal fetal specialist	4
Midwife / Physician assistant obstetrics	4
Obstetric nurse	3
Pathologist	1
Psychologist	1
Sex	
Female	38
Male	8
Age	
20-30	1
30-40	10
40-50	18
50-60	12
>60	5
Working experience	
1 to 5 years	7
6 to 10 years	5
11 to 15 years	8
16 to 20 years	4
21 to 25 years	10
25+ years	12
Any experience with premature birth in personal life or social environment	
Yes	11[a]
No	35

[a]*Experiences with premature birth: <28 weeks gestation (n=3), between 28 week-37 weeks gestation (n=5), or the gestation was unclear (n=3). The experiences were personal, in the family or with friends.*

Table 1B Demographic information of parents

Parents	**N**
Focus group interview with	
Mother	8
Father	5
Individual interviews with	
Mother	4
Father	1
Total parents interviewed	18
Participated	
Individual	12
As couple (father and mother)	3
Age in years	
20-30	3
31-40	9
41-50	5
51-60	1
Educational level	
Secondary vocational education	7
Higher professional education	7
University education	4
Experience with extremely premature birth	
>1 (imminent) extremely premature birth between GA 24+0-26+0	
Yes	2
No	13
Total cases	17[a]
Year of experience with extreme premature birth(s)	
2000-2008	2
2009-2016	4
2017-2024	11
GA at which extremely premature birth first threatened	
<23+0	1
23+0 – 23+6	6
24+0 – 24+6	5
25+0 – 25+6	2
>26+0	3
Birth between GA 24+0-26+0	
Yes	10
No, beyond 26+0	7
Multiple birth	
Yes	4
No, singleton birth	13

Table 1BContinued

Parents	N
Initial treatment decision between GA 24+0-26+0[b]	
Intensive care treatment	13
Palliative comfort care	2
Parent(s) did not make a treatment decision	2
Outcome of the premature birth[c]	
Survivor(s) (incl multiples)	12
Deceased	5
Self-reported consequences of extremely premature birth	
No consequences observed	8
Any	4

[a] *Seventeen cases of extreme premature birth includes two couples/individual parents experienced more than two (imminent) extremely premature births and 15 couple/individual parents experiencing one (imminent) extremely premature birth. Extremely premature birth of a multiple is recorded as one case.*
[b] *This includes parents who initially opted for palliative comfort care as the treatment plan until 26+0 weeks gestational age, but whose infant was born after 26 weeks.*
[c] *The outcome of premature births was categorized as either survivor or deceased accounting for both singleton and multiple births. For instance, the survivor(s) outcome encompasses singletons who survived or multiple births where both children survived*