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

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Chapter 8

# Healthcare professionals' and parental perspectives on human artificial placenta technology-trials: counselling and informed consent

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## Abstract

**Background**: The Artificial Amnion and Placenta Technology (AAPT) is developed to improve outcomes of extremely premature birth, with first in-human trials expected in the coming years. Empirical research with key stakeholders is essential for responsibly designing these trials. This study aims to discuss considerations for counselling and informed consent for the first in-human trials of the AAPT, discussing legal and ethical considerations.

**Methods**: A qualitative study using both individual and focus group interviews with HCPs and parents was performed. Interviews were thematically analysed.

**Results**: Fifteen parents and 46 HCPs were interviewed. The results are represented into key themes reflecting participants' perspectives on: (I) the moral and legal status of the subject treated in AAPT trials, (II) the first participant: the pregnant person, and (III) the terminology used to describe the technology. Furthermore, considerations around the informed consent process and counselling, including parental hope, are described. The findings suggest these factors are interconnected, as the moral and legal context surrounding AAPT trials influences the approach to counselling and informed consent.

**Conclusion**: Resolving key ethical and legal issues important for counselling and informed consent is essential for establishing parental right and the development of a responsible, ethically sound informed consent process.

## Background

The development of the Artificial Amnion and Placenta Technology (AAPT) marks a potential advancement in perinatal care, as it has been shown in animal studies to delay the transition from fetal to extrauterine physiology.[1] As such, it has the potential to reduce complications associated with extreme premature birth and intensive care treatment.[2,3] For the first in-human trials that are potentially expected in upcoming years, it is crucial to establish an adequate counselling and informed consent process including the consideration of the legal and ethical implications that play a role.[4,5]

The informed consent process for trials in perinatal care involves thorough discussions between healthcare professionals (HCPs) and parents, covering the technical aspects of the AAPT, risks, benefits, alternatives and the possibility of not achieving the intended goal.[6,7] Human AAPT trials will likely be considered in cases of imminent extreme prematurity since it is developed for this indication. Currently, prenatal counseling provides parents information based on gestational age (GA) of their infant. For delivery at the limit of viability, parents are often faced with a decision between intensive care and comfort care depending on guidelines per country. Introducing AAPT into these already complex and emotionally challenging conversations, which are often taking place under intense time pressure, introduces a new layer of complexity.[5v]

So far, research on the AAPT predominantly has focused on its technological development[3], the challenges and results observed in animal studies[8-14], and theoretical ethical and legal considerations.[15-20] There is little literature, though, about the challenges and concerns regarding the design of AAPT trials.[5,18] Additionally, research incorporating the perspectives of key stakeholders in this field is lacking. The TINY-3 study aims to fill this gap by conducting a qualitative interview study to explore the perspectives of HCPs in perinatal care and parents who have experienced an imminent or actual extremely premature birth on the future human AAPT trials. This article focuses specifically on considerations for the informed consent and counselling in human AAPT trials, as well as ethical and legal questions that play a role in the challenges surrounding counselling and informed consent.



## Methods

This research is part of the Dutch research project "Toward INdividualized care for the Youngest" (TINY-study). The TINY-3 aims to explore perspectives of different stakeholders on the AAPT as potential new treatment option for extremely prematurity. An extensive description of the methods can be found in *Supplemental material TINY-3, file 1* of this article and is also described elsewhere.[21] *Figure 1* displays the process and different phases of the TINY-3 study (*Supplemental files TINY-3, file 2)*.

In the first phase of TINY-3, a stakeholders meeting was conducted following a guidance ethics approach (*Intermezzo C*).[22] Following this stakeholder meeting, we carried out focus group discussions and individual interviews (phase 2) to further explore and expand on the main results of the stakeholders meeting.

Participants were recruited through the TINY-database with parents who have experienced an imminent or actual extreme premature birth in the past, the Dutch patient association Care4Neo, social media platforms and the researchers' professional networks. Inclusion criteria required participants to be either (I) perinatal HCPs or (II) parents who have experienced the birth of an extremely premature infant (GA <28 weeks).

An interview guide, based on the prior stakeholder meeting and the expertise of our multidisciplinary team, was developed. Interviews were moderated by 2-3 team members. Interviews were recorded and transcribed verbatim. The interviews were independently analysed and coded by AB and RK using a thematic analysis approach, following Braun and Clarke's guidelines.[23]

## Results

Six focus group interviews with HCPs (n=46), two focus group interviews with experienced parents (n=10) and five individual interviews with an experienced parent (n=5) were performed. Among the HCPs were physicians, nurses, nurse practitioners, midwives, a psychologist and a pathologist, all from the field of neonatology and obstetrics. All parents had experience with an extremely premature birth or an imminent extreme preterm birth. Demographic information is presented in *Table 1A and 1B (Supplemental files TINY-3, file 4).*

First, we present ethical and legal considerations related to counselling and the informed consent process about the AAPT: (I) the moral status of the subject inside the AAPT with the potential legal consequences and terminology, (II) the first participant: the pregnant person, and (III) the terminology of the technology. Then, we describe considerations for the informed consent and counselling including the role of parental hope. According to our participants, these themes surrounding the AAPT and its clinical trials are inherently interconnected. This directly impacts how HCPs should approach counselling parents about AAPT trials. Furthermore, this also influences how parents approach their decision-making process when considering participation.

### *Moral and legal status of the subject treated during the AAPT trials*

Parents and HCPs reflected on the subject's moral and legal status during the first AAPT trials. They emphasized the importance of establishing this status before the trials begin. All parents and some HCPs agreed that the subject should be considered a neonate, and therefore, legally recognized as being born. The following statements were presented to support this view: "*the definition of birth is the complete expulsion of the fetus from the moth-*

*er's body*", "*the baby has left the mother*", "*it is out of the mother's womb*", "*the umbilical cord has been cut*", "*it is outside the protected environment*", or "*the mother has delivered*". Parents associated 'being born' with the belief that the subject should be treated according to the rights and considerations typically afforded to any child. HCPs stated that establishing this status is crucial for clarifying the rights of the subject in the AAPT before human trials start. Furthermore, participants concluded that defining the subject as a neonate would eliminate any debate over terminology, allowing the subject to be simply referred to as a neonate. The status of 'neonate' and 'being born' was also linked by HCPs to neonatal care, thereby designating the neonatologist as the responsible HCP during the human trials. According to these participants, the AAPT should not be compared to an uterus but rather viewed as an advancement of the incubator.

In contrast, other HCPs argued that the subject in the AAPT should not be considered born, as "*it is more of a transfer*", "*the baby is not breathing*", and "*it retains the status of a fetus*". So, they suggested that it could be seen as a transfer to another fluid-based environment such as the amniotic sac and placenta, and thus falling within the field of gynecology and necessitating the involvement of gynecologists during the human trials. According to this view, the legal framework should be based on the rights of a fetus, with corresponding rights for the parents. In this context, it was suggested that developing a legal addendum specifically addressing this unique situation might provide greater safety and clarity.

One group of HCPs further debated the possibility of a 'transitional status', where the subject is neither fully born nor still a fetus. Participants stated that it would be necessary to develop a completely new legal framework, which may also lead to further discussion on the appropriate terminology to describe this transitional state.



Participants emphasized that, related to the status and corresponding rights of the (future) child, the rights of parents and HCPs should also be clearly established to protect them in decisions regarding the initiation or withdrawal of treatment during the human trials.

### *The first participant: the pregnant person*

Especially HCPs worried about the first participant in the context of AAPT trials: the pregnant person. HCPs stressed that pregnant persons may be willing to accept significant disadvantages for themselves for the sake of their baby, far more than what we would ask of other patients, "*such as organ donors*". Furthermore, they were concerned whether you could ask a pregnant person to undergo a cesarean section to participate in the AAPT trial, without knowing the benefits for the subject. Some HCPs emphasized the damage that would be done to a woman and potential future children. As one HCP stated: "*I wonder if it's a promising development for the mother, especially considering the potential implications for following pregnancies if she undergoes a cesarean section at 24 weeks*". One HCP also noted that when parents opt for comfort care, a cesarean section is typically not performed. Some of the mothers were not willing to undergo a cesarean section or doubted if this

would be desirable in all situations. These concerns of participants made clear that the informed consent for mother and child are intertwined and some suggested two sequential informed consents.

### *Terminology to describe the technology*

During discussions on the moral and legal status of the subject undergoing treatment in the AAPT, it became evident that this is also connected to the terminology being used. Participants reflected on whether labeling the AAPT as either a placenta or an uterus might shape the perceived nature of the technology, potentially influencing how we view the moral and legal status of the subject. In contrast, if the AAPT were considered an incubator, the subject might be viewed as a neonate. Moreover, a mother mentioned the terminology being important for the acceptance of the technology: "*When I first read about it, my immediate feeling was a bit like: I would replace the word 'artificial.' [...], I notice that people, myself included, tend to be kind of deterrent, because artificial is so distant from emotion and humanity*".

### *Informed consent and counselling*

Participants discussed what they considered essential in the informed consent and counselling about the AAPT trials. Parents emphasized that the informed consent about the AAPT-trial should be "*good, objective and personalized*".

First, conditions for the process of counselling and informed consent were discussed. HCPs considered it important to estimate if parents could comprehend what participating in a trial with the AAPT would mean, which includes parents understanding the language and being able to understand all the information. Furthermore, both parents and HCPs agreed that time to counsel parents is essential, preferably time to counsel parents more than once, for parents to consider the decision about participating in first in-human trials carefully, and for involving other disciplines. As one parents stated: "*[Counselling should not take place] at the most urgent moment, but [should take place] when you have a more calm feeling, so that you also have time to take a look at the information about the AAPT*". It was suggested that parents would be counseled during a high-risk pregnancy about the human AAPT trials in the event of extreme premature birth, or that the research population be adapted to include individuals who would have sufficient time for counseling.

Furthermore, it was discussed how the option of human AAPT trials would fit in the current counselling and decision between early intensive care treatment and palliative comfort care. Some participants thought it should be given as an additional option alongside intensive care and palliative comfort care, while the others preferred to present the option of the AAPT trial only after parents opted for intensive care treatment. In *Table 2*, the different reasons per option are summarized supported by quotes. *Figure 2* gives an overview of these different pathways. Notably, there was no mention of discussing AAPT after parents had made the decision to opt for palliative comfort care. Participants agreed there should

be one universal approach for counselling parents and the moment to present the option of the AAPT trials.

**Table 2** The timing of offering the option to participate in the human trials of the artificial amnion and placenta technology

| Moment of giving the option to participate in the human trials of the AAPT | Reasons of the participants |
|---|---|
| **AAPT trial as option in addition to intensive care treatment and palliative comfort care** | **Been given all the options:** "*I would have wanted to know [all the options]. (...) Even if you choose not to, I still would have wanted to know. That you have those three options" [*parent] |
| | **Try the artificial placenta instead of comfort care: "***If someone chooses palliative care, but still wants to try the artificial placenta, you never know how it may change the parental perspective. If they decide for AAPT and see after a few weeks: it's going well in the AAPT, maybe they will opt for active treatment afterwards***"**[HCP] |
| | **Different treatment**: "*[The trial with the AAPT] is really different from the current treatment we are providing [in case of starting intensive care treatment] now*" (HCP) |
| | **Intensive care treatment in case the AAPT fails:** "*It is an option alongside intensive care treatment and comfort care, because if AAPT doesn't work, then you can still [stop with the trials and] switch to intensive care treatment, [so it is not a decision between treatment with an incubator, or with the AAPT].*" [parent] |
| **AAPT trial as option after decision intensive care treatment** | **Unknown outcomes:** "*..because you don't know yet what it's going to be, what the outcomes will be in the AAPT*" [parent] |
| | **Clear decision:** "*That parents at least have the choice not to go down that path, and that it's clear whether it's left or right. With one, you treat, with the other, you don't*" [HCP] |
| | **Form of active care:** "*but for me, it falls into that active care category*" [HCP] |
| | **Confusing to give another option: "***So comfort care or active care. And then from there explain the difference between those two. Otherwise, you really can't see the forest for the trees, right?"* [HCP] |

*Abbreviations: AAPT = artificial amnion and placenta technology; HCP(s) = healthcare professional(s)*

Second, conditions for the content of the counselling were formulated. Parents and HCPs agreed it was essential to be honest about the experimental character and the lack of long-term data about the effects of this treatment. Moreover, the role of parents during the AAPT-trial, the need for a cesarean section with the additional uncertainty about the timing of delivery and the associated risk of a medically induced early delivery, and what to expect during treatment (e.g., possibility to touch your infant) should be discussed to prepare parents according to both parents and HCPs. Parents were opposed to discussing the risks based on the animal testing model for those who want to know statistics. Other participants were uncertain about whether you should mention this, especially about when you should bring it up during counselling: "*That's probably a very strange moment when you*

*suddenly start talking about animals. [...] For people who like to hear the numbers, that might be something... But it's really difficult, because when do you bring that up?"*

Lastly, the discussion focused on potential considerations for parents regarding participation in human trials, as presented in *Table 3*. Parents felt it would be an impossible choice, because neither short-term nor long-term data could be considered, given the fact that the AAPT had not yet been tested on humans. Parents worried about the emotionally overwhelming state when they faced an imminent extremely premature birth. They had based their decision when facing their imminent extremely premature birth on the instinct to save their child. One parent felt that parents could not be asked to make this decision.

### *Parental hope*

Some parents favored the information about the potential benefits of the AAPT for their child. In the absence of specific statistics and probabilities, they speculated that the potential outcomes of the AAPT could be more favorable than those of current treatments. HCPs could envision parents viewing this decision as a matter of life and death, believing that the AAPT might offer the best chance for their child's survival or believing that it would be the 'better' option.

*Figure 2* gives an overview of these different pathways. Notably, there was no mention of discussing AAPT after parents had made the decision to opt for palliative comfort care. Participants agreed there should be one universal approach for counselling parents and the moment to present the option of the AAPT trials.

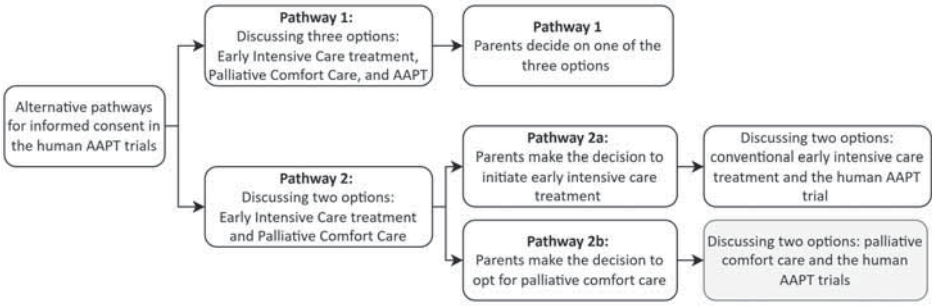


**Figure 2** An overview of the different consent pathways, including, in grey, the pathway that was not discussed by the participants but could theoretically be an option in the context of 'nothing to lose'. The fact that the pathway via palliative comfort care was not mentioned may be attributed to the way the interviews were conducted, as in some interviews participants spontaneously brought up when this should be offered, while in others the interviewers had to ask about it explicitly, which may have caused a probing effect.

**Table 3** Pro and contra arguments of parents whether they would be willing to participate in human artificial amnion and placenta technology trials

| Pro | Contra |
|---|---|
| **AAPT may give a better outcome:** "*It comes down to the fact that we had already decided that [child's name] was going to pass away. (...) You could take the chance. The outcome was already negative, so it can only get better*" | **Experience with good outcome after current treatment:** "*With my background, I think I wouldn't choose this in the experimental phase, because I know it can also go well at 24 weeks.*" |
| **Risk of the cesarean section is acceptable because this decision is for this child, not for future children:** *"[This is about your child right now.] Whether there comes a brother or sister at a later moment, you would never know that. That's not a given fact. But if you can save these children with it: bring it on"* | **Cesarean section:** "*If a C-section needs to be done, it apparently isn't good for the next pregnancies. If it's the first time, with a premature birth, then I wouldn't do it"* |
| **Trust in medical science: "***Trust that this has been carefully thought through, so let's give it a try because the situation is already unpromising"* | **No long-term data/to risky:** "*You decide to take a great risk with a treatment [in a trial setting] of which nothing is known yet*" |
| **To create statistics for others in the future:** "*For me, I would like to contribute to actually creating statistics for the future and maybe you also benefit from it with your own child*" | **Own good experience:** "*I was in an incubator myself and turned out well. [So I would go for] the safe option*!" |
| **To prevent suffering associated with the conventional NICU-treatment:** "*So much is already asked of a baby at 24 weeks; laying in the incubator, with lots of injections, and the struggle to breath, with the potential risk to have to go back on the ventilator. (...) And if they could just rest in something like a womb-like environment for another four weeks, where they don't have to breathe and aren't poked from all sides, just can grow, wouldn't that be much better?"* | **Test baby:** "*Not wanting to be the 'first test baby'* |
| **No disadvantages:** *"No known disadvantages."* | |

Abbreviations: AAPT = artificial amnion and placenta technology.



## DISCUSSION

This article focused on the stakeholders' formulating considerations pertaining to the informed consent and counselling surrounding AAPT trials in humans. In this discussion section, the impact of the AAPT on existing concepts and boundaries in the context of extreme premature birth are presented and challenges in counselling and informed consent are further discussed.

### *Changing boundaries and concepts*

With the introduction of the AAPT, the (ethical) landscape of managing extreme prematurity may fundamentally change. Existing concepts (e.g., being born or not) and used terminology (e.g., neonate or fetus) may no longer adequately capture the complexities introduced

by the AAPT, as these terms often imply moral boundaries that the AAPT challenges.[15-17] Our results reveal a tension between how parents and HCPs perceive these concepts. All parents tended to view the child as "born," which is understandable given the difficulty in perceiving infants who have left the womb as anything other than being born. In contrast, some HCPs saw the status of the subject in the AAPT as 'not being born/a fetus', which could mean parents have to reframe their entire process and experience of birth into a different category. This view of the subject having the moral status of a fetus would not change anything in the legal position of the subject after transferring from the womb to an AAPT.[15,17,19] A fetus is not legally recognized as born and therefore has no independent rights.[19,24,25] However, it could impact the distribution of parental rights. In most countries the rights of a father change when the child is legally born.[19,26] Furthermore, the notion that the pregnant person's bodily autonomy remains the central determining factor for the subject that is no longer inside the pregnant person but also not legally born yet, becomes harder to justify, raising questions about the balance of rights in this unique context and the potentially need of an addendum to the law. Lastly, referring to the subject as "born" may be more straightforward, as parents are likely to view the subject as their child, and an established legal framework would already be in place.[19,27,28]

For the design of the AAPT trials, and consequent counseling and informed consent, it is crucial to have a clear understanding of the ethical and legal position of the patient(s) in the trial, the technology and the responsibilities and rights of all involved parties.[5] Without establishing this beforehand, it would be difficult to effectively communicate with parents about AAPT trials and what participating in a human trial means legally.

### *Challenges in the informed consent and counselling*

After discussing moral and legal challenges surrounding the informed consent, it is essential to look at the process and content of the counselling and informed consent. Generally, consent for participation in clinical research is considered valid when the following criteria are met: competence, information, understanding and voluntariness.[29] The conditions formulated by our participants – 'ensure parents can fully comprehend the information provided' and 'allow sufficient time to counsel parents' – emphasize these widely accepted requirements for informed consent in medical research. For disclosure of sufficient information, participants believed a certain minimum amount of information should be provided to parents during counseling about the trials, such as the experimental character, lack of short- and longterm data, the role of parents during the trails and the necessity of an cesarean section. Meeting these criteria could be challenging and difficult to assess.

Our participants' considerations of the informed consent for the human AAPT trial are underscored by those of other high-tech medical perinatal trials, such as the Management of Myelomeningocele Study (MOMs) trial and Extra Corporeal Life Support (ECLS) trials.[6,30-32] These trials also show the importance of having time to counsel parents, to start counseling in time (e.g., during high risk pregnancy) and to select the research population based on

the established fundamental conditions for counselling and informed consent.[30,32] With the MOMs trial, parents benefitted from discussing their moral concerns during ethical consultations as part of counselling and informed consent, highlighting the advantage of a multidisciplinary approach.[33] The ECLS trials provide valuable lessons on complexity of information, especially in such emotional overwhelming situations, which could lead to the misunderstanding of parents about the nature and purpose of the trial.[34] Both trials also discussed concerns about voluntariness and maternal well-being indicating parents viewed consent requests as an implied preference for the new treatment, leading them to feel they had no choice but to consent due to the lack of alternative options.[35,36] The way consent is requested can lead parents to feel that a treatment—like ECLS, which could be lifesaving—is the only acceptable option, leaving them no choice, even though consent should be fully voluntary.[36] Furthermore, the MOMs trial demonstrated that pregnant individuals were often willing to take on significant personal risks during pregnancy to benefit their unborn child.[31] Finally, literature on complex decision-making in pediatrics indicates that parents find sharing responsibility in decisions particularly challenging in highly technical and urgent situations.[37,38]

These high-tech medical perinatal trials provide some guidance for the informed consent in the AAPT context, such as the recommendation of a multidisciplinary approach and addressing challenges in voluntariness and the pregnant person as participant in a trial. However, other significant challenges remain such as the complexity of the information and the timing of consent, and ongoing discussions are essential to find solutions, make recommendations and develop a comprehensive informed consent process. Evaluating and updating the counselling and the informed consent should also be an essential part of the human trials.



As parents and HCPs navigate these high-stakes decisions, it may be necessary to adapt existing counselling informed consent processes.[39-41] The emotional stress, technical complexity, and urgency of the intervention may hinder complete disclosure and increase the risk of therapeutic misconception.[42,43] Parents may favor the potential advantages over disadvantages, misunderstanding that clinical research aims to generate generalizable knowledge, rather than individual benefit.[44,45]

### *Potential therapeutic misconception*

The results show the inherent difficulty of separating a research setting from a care setting in the context of the AAPT. Both the answers from parents and HCPs reflect this challenge, as their responses often seem to be shaped by the expectation—or at least the hope—that participation in the human AAPT trials would yield personal benefits for the child involved rather than to advance scientific knowledge. This concern is also described in literature as therapeutic misconception. Therapeutic misconception may constitute (I) an unrealistic expectation of personal benefit, based on misunderstanding of the nature of the clinical trial or (II) the failure to realize that research is the primary purpose of the clinical trial.[46]

Thus, it is essential to clearly differentiate between the goals of clinical research and standard therapeutic treatment.[47] Furthermore, it should be explicitly communicated that the trial's primary aim is to gather knowledge, which may not directly benefit the patient, while standard treatment focuses solely on the patient's care.[48] Furthermore, providing enough time for discussion and reflection can also help mitigate the pressures that might lead to therapeutic misconception.[49] By implementing these strategies, the likelihood of therapeutic misconception can be reduced and the informed consent process for AAPT trials would be aligned with the best practices learned from similar research.

### *Strengths and Limitations*

This study has several strengths. It is the first qualitative paper providing a unique insight into the perspectives of HCPs and experienced parents regarding the AAPT trials. The TINY-3 study benefits from a diverse selection of participants giving a broad range of perspectives on the development of the AAPT. Additionally, the multidisciplinary research team adds to the strength of the study by interpreting the results from different perspectives.

However, there are also limitations to consider. Firstly, certain findings may be influenced by the specific Dutch context and societal values, potentially limiting the perspectives on this technology to the Dutch perspective. Secondly, the recruitment process predominantly attracted HCPs working at the NICU. Despite the apparent achievement of thematic saturation, it remains unclear whether the obstetrical and neonatal perspectives were equally represented. While the overall number of parents that were interviewed seems limited, we were able to interview parents with varying backgrounds and experiences, resulting in a range of perspectives from experienced parents that contributed to data saturation. Additionally, individuals with strong negative opinions about this development may have been more inclined to volunteer for the study, potentially biasing the results.

## Conclusion

This article offers insights into stakeholders' perspectives on counselling and the informed consent related to future human AAPT trials, discussing ethical and legal considerations and complexities. The discussion about the moral status of the subject in the AAPT underscores the need for consensus on important concepts before proceeding to further designing the human AAPT trials. Resolving such matters is crucial for defining legal challenges like the rights of all involved parties in potential future trials, and therefore the process of counselling and informed consent. The complexities of these issues make it clear that the discussion around informed consent must be handled carefully with all stakeholders involved. Ongoing dialogue is essential to develop a responsible and ethically robust framework for counselling and informed consent for the human AAPT trials.

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