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<https://doi.org/10.1057/s41599-022-01167-8>

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Dutch perspectives on the conceptual and moral qualification of human embryo-like structures: a qualitative study

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The number of publications on the governance of research with human embryo-like structures (hELS), i.e., 3D aggregates of human (induced) pluripotent stem cells made to model early human development, is growing rapidly. Public involvement is called for in many of these publications, but studies on public perspectives towards this emerging field remain lacking due to its novelty. To reduce the gap in the literature and contribute to the ongoing scholarly debate, we conducted interviews with Dutch lay citizens, health law and health care professionals, and interviewees reasoning from prominent worldviews in the Netherlands. This article reports on these participants' views about the conceptual and moral qualification of hELS. With regard to the conceptual qualification of hELS, participants believed it should provide a shorthand for their (dis)similarity to human embryos, but differences remained with regard to the features upon which this (dis)similarity should be based. With regard to the moral qualification of hELS, participants believed this should depend on whether or not hELS possessed the features they considered morally relevant, among which those associated with sentience and a potential for continuous human development. Taken together, these findings align well with the arguments and positions traditionally found in related ethical debates and the recently proposed recommendations for the governance of research with hELS specifically. As such, they may also help allay concerns about lay publics not being able to meaningfully participate in debates about the ethical ramifications of (novel) scientific developments.

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Introduction

The growing interest in human embryo-like structures (hELS), i.e., 3D aggregates of human (induced) pluripotent stem cells, is driven by the belief that they come sufficiently close to human embryos to complement their research use, while remaining sufficiently different from them to circumvent the technical, legal, and ethical sensitivities of human embryo research (Rivron and Fu, 2021; Rossant and Tam, 2021; Posfai et al., 2021; Mummery and Anthony, 2021).

Despite the growing stream of academic publications on the science and governance of this emerging field (Hyun et al., 2020; Pereira Daoud et al., 2020; Sawai et al., 2020; Clark et al., 2021; Matthews et al., 2021), little is known about public perspectives on the conceptual and moral qualifications of hELS, and on what this should entail for the use of these structures in research. Our empirical study aims to reduce this gap in the literature and to contribute to the ongoing scholarly debate by probing these issues through the lenses of lay citizens, health law and health ethics professionals, and individuals reasoning from prominent worldviews in the Netherlands.

In this paper, we first describe our methods, including the sample, setting, and analysis of the research data, after which we report on the findings pertaining to the participants' conceptual and moral qualification of hELS, respectively. This division between 'concepts' and 'morals' is merely pragmatic: we are of course aware of the interconnectedness between the descriptive and the normative, and by no means wish to purport that the two can be strictly untangled. In the section "Discussion", we bring these results together and illuminate the areas of common ground and those that prompt debate. We conclude by relating these findings to recent guidelines and pinpointing issues in need of further enquiry.

Methods

This paper is part of a larger study in which we explore the range of professional and lay perspectives on the creation and research use of hELS. Data were collected between August 2020 and March 2021 in the Netherlands. The full data set consisted of three focus group interviews with a cross section of the Dutch public, one focus group with health law and health ethics professionals, and

five in-depth interviews with individual representatives of prominent worldviews in the Netherlands (CBS, 2020) (for the full research sample, see Tables 1–3). In this article, we report on the findings pertaining to the participants' conceptual and moral qualification of hELS.

Research sample and setting. The four focus group interviews ($N = 33$) were held in August and September 2020 and lasted two hours on average. Three of these were conducted with lay citizens. The lay citizens in the pilot focus group (FG-PILOT, $n = 5$) were selected from the network of APD based on the demographic characteristics (sex, age, education level) of the Dutch population and invited personally. For the other two focus groups with lay citizens (FG-LAY1, $n = 10$ and FG-LAY2, $n = 11$), we hired a recruitment agency to select a representative cross-section of the Dutch population. Participants in these groups received a small (€50,-) financial compensation. The fourth focus group interview (FG-Professionals, $n = 7$) was conducted with health law and health ethics specialists selected from the networks of the authors, based on the participants' affinity with debates on the ethical, legal, and societal implications of comparable emerging biotechnologies.

Considering that perspectives on human embryo research can be strongly intertwined with (non-)religious worldviews, and assuming that the same may hold true for research with hELS, five in-depth interviews were conducted with interviewees known to reason from worldviews prominent in the Netherlands (Catholicism, Protestantism, Judaism, Islam and Humanism) and familiar with related bioethical debates. The aim of these interviews was to supplement the data gathered in the focus groups. These interviews were held between August 2020 and March 2021, lasted one and a half hour on average, and were held online via *BlueJeans*.

Data collection and analysis. For consistency, focus group and individual participants received the same invitational letter and set of semi-structured questions. These open-ended questions (see Supplementary Information) were formulated in ways that allowed participants to expand on topics they personally

Table 1 Research sample of focus groups with lay participants.

Type	Sex	Age	Educational level ^a
FG-Pilot ($n = 5$)	2/5 male 3/5 female	3/5 = 20 ≤ 30 years old	2/5 ≤ MBO 2/5 = HBO 1/5 ≥ WO
		0/5 = 30 ≤ 40 years old	
		0/5 = 40 ≤ 50 years old	
		1/5 = 50 ≤ 60 years old	
		1/5 ≥ 60 years old	
FG-Lay1 ($n = 10$)	6/10 male 4/10 female	3/10 = 20 ≤ 30 years old	6/10 ≤ MBO 2/10 = HBO 2/10 ≥ WO
		2/10 = 30 ≤ 40 years old	
		1/10 = 40 ≤ 50 years old	
		1/10 = 50 ≤ 60 years old	
		3/10 ≥ 60 years old	
FG-Lay2 ($n = 11$)	5/11 male 6/11 female	1/11 = 20 ≤ 30 years old	5/11 ≤ MBO 2/11 = HBO 4/11 ≥ WO
		4/11 = 30 ≤ 40 years old	
		2/11 = 40 ≤ 50 years old	
		0/11 = 50 ≤ 60 years old	
		4/11 ≥ 60 years old	
TOTAL ($n = 26$)	13/26 male 13/26 female	7/26 = 20 ≤ 30 years old	13/26 ≤ MBO 6/26 = HBO 7/26 ≥ WO
		6/26 = 30 ≤ 40 years old	
		3/26 = 40 ≤ 50 years old	
		2/26 = 50 ≤ 60 years old	
		8/26 ≥ 60 years old	

^aEducation in the Netherlands discerns between Middelbaar Beroepsonderwijs (MBO, secondary vocational education), Hoger Beroepsonderwijs (HBO, higher professional education), and Wetenschappelijk Onderwijs (WO, higher scientific education).

Table 2 Research sample of focus group with professional participants.

Type	Sex	Age	Expertise
FG-Professionals (n = 7)	2/7 male	0/7 = 20 ≤ 30 years old	4/7 health ethics
		5/ 7 female	1/7 = 30 ≤ 40 years old
		3/7 = 40 ≤ 50 years old	
		1/7 = 50 ≤ 60 years old	
		2/7 ≥ 60 years old	

considered important whilst still probing the ethical and policy issues we had previously found to be in need of further enquiry (Pereira Daoud et al., 2020).

The interviews, held in Dutch and audio recorded, were transcribed *verbatim* and pseudonymized for thematic analysis. Interviews with participants reasoning from prominent worldviews were additionally summarized and sent to the respective participants for approval. Considering the explorative nature of our study, the first step in our thematic analysis was to create open codes that tentatively labelled important passages. These codes were created in *Atlas.ti 8* by APD. After the full list of open codes was validated by WD through a randomized sampling method, APD clustered them in a mind map based on the questions to which they were related. The resulting clusters were evaluated and adapted in meetings with the research team until higher order themes could be consistently agreed upon by all members. The thematic data analysis resulted in four themes, two of which we discuss below.¹

Results

The conceptual qualification of hELS: origins and potentialities. An important topic in relation to hELS is what language we should use to refer to them. At present, various *general, developmental time-based,* and *cell-based* names (Matthews et al., 2021) co-exist in an effort to denote these structures and the particular differences between them. In what follows, we elaborate on the participants’ perceptions of prominent umbrella terms and the features that they considered key in developing appropriate terminology for hELS.

Focus group interviews. When asked which of two general terms—i.e., ‘synthetic embryos’ or ‘embryo-like structures’—the participants preferred to denote hELS, neither term was overwhelmingly favoured. Both were considered misleading, albeit for opposite reasons. The term ‘synthetic’ was viewed as delusive because it ‘dehumanized’ the models in question. For several participants, ‘synthetic’ invoked the impression that “you could create [hELS] from stuff you can find on the kitchen table, so to speak”, thus making it “very unclear that it consists of human components.” By contrast, the term ‘embryo-like’ was viewed as misleading because it allegedly prematurely prompted people to “immediately think, ‘oh, it is a human being; oh, it is an embryo’.”

Participants were noticeably mindful of the impact these perceived connotations could have in steering public opinion. They worried particularly that vague, general terms may pre-empt the ability to form an opinion. One of the professionals, for instance,

“...struggle[d] a lot with the word ‘embryo-like structure’ because all kinds of things could fall under it (...) and with that, it becomes a black box [to determine], what exactly are

Table 3 Research sample of individual interviews.

Type	Sex	Worldview
Individual Interviews (n = 5)	4/5 male	4/5 religious (Catholicism; Protestantism; Judaism; Islam)
	1/5 female	1/5 non-religious (Humanism)

scientists doing in the lab? And how can we societally and democratically find something of it? With those kind of container terms, that is all covered up.”

Bearing these connotations in mind, we asked lay and professional groups to consider how they would define hELS vis-à-vis human embryos. Here, two contrasting attributes—*origins* and *potentialities*—were key, with neither group having a clear preference for one of these attributes.

On the one hand, were participants claiming that appropriate terminology should reflect the *origins* of hELS; i.e., how they came into being. As argued by two professionals, for instance, “I would think [that] an embryo—actually, my first intuition is then that a sperm cell and an egg cell got together. To me, that is then an embryo”, which would imply that hELS are categorically different from embryos. In lay groups, this view was even more pronounced. Here, several lay participants argued that an embryo “is created from fertilization and that [a hELS] is created from stem cells—and there is a difference”, or that the difference between a “‘natural’ embryo, [which originates] from two unique gene sets, or a clone-embryo” must be clear.

On the other hand, were participants that believed appropriate nomenclature should denote the expected *potentialities* of hELS; i.e., that it should reflect their “viability” or “potential to grow into a human being”. As argued by professionals, “...my gut-feeling would be that [an embryo] is a human being in the making”, and “the moment that you can actually create something with those embryo-like structures—an entity that, if implanted, could [grow into] a human being—that is, at least morally, (...) very relevant.” Similarly, lay participants argued, “...if you think of an embryo (...), then [you think of] the creation of a baby, so that’s what you assume, regardless of how small it is”, and “if [a hELS] could potentially go through [embryonic] development, then it is an embryo”.

The difficulty of reaching consensus on whether hELS qualify as (non-)embryos seemed to be—at least partly—the consequence of current embryo definitions, which one professional succinctly summarized as

“... a tablecloth that is too small to cover the table. If we pull it in the direction of fertilization, we’ll have a table not fully covered because [it leaves us with] cloned structures. If we draw it towards (...) the potential to develop into a human being, I think we also have a problem because (...) then it is very difficult to speak of non-viable embryos.”

Individual interviews. Most interviewees had no strong terminological preference either. In fact, from those reasoning from religious worldviews, the Protestant interviewee was the only one to explicitly prefer ‘embryo-like’ over ‘synthetic’. Like some focus group participants, this interviewee felt that ‘synthetic’ may be too ‘dehumanizing’ in the sense that it can evoke the idea that these structures are ‘not real’ and, therefore, be taken to prematurely imply that they cannot matter morally. Simultaneously, it may be too ‘anthropomorphic’ in the sense that it could be taken to mean that these structures *are embryos* in the morally relevant ways—albeit embryos that were created through artificial means.

Terminology that would prematurely imply the latter conclusion was deemed inappropriate by all interviewees reasoning from religious worldviews. Driving these intuitions was the view that the key denominator between embryos and non-embryos should be their potential to develop into a foetus and then into a child, which was understood as denoting the continuous development of the human being *that the embryo already is*. This is also why these interviewees explicitly referred to human embryos as ‘human beings in the making’, ‘human beings embodying themselves’, or as ‘specimen of their kind’.

By contrast, the interviewee reasoning from a Humanist perspective was the only one to lean towards defining the human embryo in terms of how it usually comes to be—i.e., the process of fertilization. hELS that come so close to fertilization-derived embryos that they are functionally indistinguishable from them could then be denoted as ‘artificial embryos’, whereas those that come less close might be referred to as ‘embryo-like’ structures. This interviewee stressed the ethical importance of holding on to conceptual ambiguities as arising from technological developments such as those in this field, noting that the resulting moral ambivalence is something to be faced rather than avoided.

The moral qualification of hELS: moral status and beyond.

Another currently discussed issue in relation to hELS is whether they can provide a morally preferable alternative to research with human embryos (Rivron et al., 2018; Wilger, 2019; Nicolas et al., 2021; Rossant and Tam, 2021; Posfai et al., 2021; Moris et al., 2021). To probe the participants’ views on this topic, we developed two practical exercises, which we discuss separately below.

The moral protection due to human and non-human organisms: exercise I. The first exercise asked participants to place ten distinct living organisms in pecking order; the higher their rank, the more protection they should be afforded. These organisms were (in no particular order): a human zygote, a human embryo (of roughly 8 weeks), a human foetus (of roughly 24 weeks), a mouse, a chimpanzee, a toddler, an adult person, a fish, a tree, and a human gastruloid. The ‘human gastruloid’ was included as a concrete example of ELS due to it being one of the first types created from human stem cells at the time. The further particularities of ‘gastruloids’—such as their lack of extraembryonic cells and, therefore, incapability of continuing integrated human development—were not further discussed, thus purposefully leaving open the question whether or not hELS could (come to) have the potential to develop into human beings.

Focus group interviews

Most participants preferred to group several organisms together, thereby creating threshold-based rankings. In these groups, the adult and toddler structurally shared first place, after which the foetus often immediately followed. The mouse and fish were often also grouped together, generally taking a middle-low position in the rankings. At the bottom of most rankings, were the tree and gastruloid, though the gastruloid was more often viewed as being due greater protection than the tree. In fact, for two lay participants, the gastruloid was due the same protection as any other human organism, thus sharing first place with the adult, toddler, foetus, embryo, and zygote. The chimpanzee, embryo, and zygote were clearly borderline cases, with most participants struggling to position them in the ranking (between high and middle-high), though more often conferring greater protection to the chimpanzee, then to the embryo, and then to the zygote, respectively.

A recurring consideration underlying these rankings was that sentient beings deserve at least *some* protection. As explained by one of the lay participants:

“I think that ethics depends on the [capacity to feel]. We would not need to (...) have a discussion about bricks. Because bricks are bricks, right? But the moment a living entity can feel, then you can start to wonder how you should treat it.”

For some participants, a ‘capacity to feel’ (or: sentience) was the single most important basis for affording protection. Others came up with more elaborate distinctions between sentient beings, distinguishing between those with a mere physiological capacity to feel pain, and those capable of more complex forms of self-awareness. As continued by the participant quoted above, for instance:

“You know, another criterion is whether the being in question (...) is conscious of its situation. (...) I think a chimpanzee is more aware of his environment than a fish (...). So the chimpanzee can estimate for himself whether he is in a situation in which he is happy or in which he suffers.”

The question whether the zygote, gastruloid, and embryo met this criterion—even if only in a rudimentary sense—sparked debate in lay groups. For some, the early developmental stage of the zygote and hELS was perceived as evidence that they cannot be sentient at all, and therefore reason to confer them the least protection. From this, it followed that the (degree of) protection afforded to embryos would equally depend on their ‘capacity to feel’, which prompted discussions about neural development and brain activity at this stage in embryogenesis.

Simultaneously, the fact that several participants conferred greater protection to embryos and foetuses (and, in some cases, to the zygote and gastruloid) than to most (and, occasionally, all) non-human animals, reveals that considerations other than sentience must also have been at play. Some reasoned, for instance, that human organisms should be given precedence over non-human organisms simply because they are human:

“It may sound very blunt, but we’re talking about an animal or a human being. (...) I think that... Well, it is human. While actually precisely the same worth—in terms of life—[is at stake], eventually it is the last one standing that wins.”

Others reasoned that the relatively higher protection afforded to embryos and foetuses had to do with their special potential toward further human development:

“An embryo develops—in the ideal situation (...)—into a human being. And then you have [to consider] the worthiness [of the embryo] at present, but you also have [to consider] the worthiness [of the embryo] in terms of [its] potential.”

For one of these participants—who, under explicit reference to that ‘special potential’, attributed maximum protection to all human beings—the question whether that protection should extend to hELS would thus depend

“...on whether you can define it as an embryo or not. I think [that] if you can define it as an embryo, or at least as ‘embryo-like’, then I think it has as much worth, intrinsically, as a human adult.”

While this participant argued that, if hELS had this potential, they would be due (full) protection throughout, others felt it did make a difference that it was only the early stages, as compared, for instance, to a foetus.

Finally, participants also suggested that hELS deserve a lower ranking in view of their explicit research purpose. For instance: “That embryo-like structure has been created in a lab somewhere. With the purpose, I presume, to do research. And then I find that purpose more important than the purpose of the embryo to [grow into a human being].” Connected with this was their artificiality and easy replaceability:

“...at the bottom is the embryo-like structure. Because, for me, it comes from a laboratory and is, as it were, subservient to what we want to know and what we can do with it, and so on. So it’s really different for me. (...) That [hELS] we can basically just throw in the trash. (...) I have (...) instinctively much more respect for that oocyte and that embryo than for that embryo-like structure.”

When we asked whether this participant would think differently if hELS could grow into human beings, the answer was still ‘no’ because the resulting clone would be an artefact: “... even then, it would not be a real human being in my view, because it originates from an existing DNA”. Similarly, a professional who accorded the highest ranking to “everything that is or can become a human being” did not reason that hELS—if capable of growing into a human being—should be on the same level. Instead, the professional placed such hELS still “somewhat (...) lower because they are more artificial”.

Individual interviews

The interviewees reasoning from a religious worldview conferred the highest degree of protection to all (potential) human beings, i.e., the adult, toddler, foetus, embryo and zygote. Next came the fauna, with the chimpanzee ranking highest amongst the non-human animals. For these interviewees, the ranking of the gastruloid was conditional on its potential to develop into a human being. If we were to assume that gastruloids have this potential, then they would all rank it as a human being and confer it maximum protection. If we were to assume that gastruloids do not have this potential, then their ranking would be lower. Whereas interviewees reasoning from a Catholic, Protestant, and Jewish perspective would place it below the flora, and thus confer it the least degree of protection, the interviewee reasoning from an Islamic perspective would rank it between the human and animal categories, thus conferring it a middle-high degree of protection.

Of note, the interviewee reasoning from an Islamic perspective argued that, even if hELS could one day acquire a capacity for further development, this would still be an artificially acquired capacity, rather than an autonomous or inherent one. From this, it followed that research with hELS would be preferable over research with embryos—even if both were capable of developing further. The interviewees reasoning from a Christian and Jewish perspective did not discount the possibility of hELS one day acquiring the autonomous or inherent potential to develop into (or: *as*) a human being. Instead, they stressed that, with science moving forward, the problem is that one cannot know with certainty—nor establish in ethically acceptable ways—whether or not improved variants of hELS may have this potential. When asked their thoughts on the possibility of averting this uncertainty by programming so-called ‘suicide genes’ so as to make hELS incapable of further human development, all three interviewees—although most emphatically those reasoning from a Christian perspective—argued this would be paradoxical: would suicide genes really prevent hELS from acquiring the relevant potential, or would they merely frustrate it? For those reasoning from a Christian background, the only way to deal with this

epistemological uncertainty was therefore to err on the side of safety and simply not create hELS.

The interviewee reasoning from a Humanist perspective was the only one to diverge from the ‘(potential) humanity > fauna > flora’ outline. In her/his ranking, the adult, toddler and chimpanzee were afforded maximum protection, after which followed a separate category for the foetus. In third place, came the fish, mouse, and tree. Finally, at the bottom, and due the least protection, were the embryo, zygote, and gastruloid. Though this interviewee struggled to pinpoint the exact reasons for this ranking, an important consideration seemed to be that the “more complex and communicating” the organism, the greater the protection they should be afforded.

The moral protection due to early human organisms: exercise II. In the second exercise, we asked participants to evaluate three hypothetical research proposals as if they were members of a hospital’s ethics committee. These proposals involved research with surplus human embryos, human embryos specially created for research (‘research’ embryos)², and hELS. The aim of these (hypothetical) scenarios was to enquire the participants’ perspectives on embryo research and ensuing implications for research with hELS. The research proposals were imagined to meet the relevant legal requirements, to be methodologically sound, and to potentially provide relevant new insights to the improvement of in vitro fertilization (IVF).

Focus group interviews

The hypothetical research proposal with surplus embryos did not spark any significant debate among professionals, who argued not to see the problem of such research if conducted under current legal conditions. In lay groups, however, there was debate. For many, surplus human embryo research was perfectly acceptable if the proposal were sound and seriously considered, the idea being that “the benefits of [surplus embryo] research prevail” for several reasons. Arguments were that surplus embryos “are already here anyway, so (...) if we already have them, it’s better to do something useful with them than to just throw them away”, that embryos at these stages “are not yet so far developed that you could say you are really harming them”, and that research aimed at improving IVF was considered a worthy end. But in every lay group, there was also at least one participant conveying the view that even though surplus embryo research “is [legally] allowed, (...) I don’t think it should be”. In fact, one of these participants was

“...actually a bit shocked that there even are surplus embryos at all. And that they are then destroyed. (...) I get that it is reasoned that, if they are to be destroyed anyway, then so be it; do research with it. But I would actually prefer that there aren’t any spare embryos to destroy or do research with at all.”

For this participant, the main reason to reject surplus embryo research was the view that “there is an intrinsic value to embryos, whether they are surplus or not”, and that recognizing that value would mean recognizing that they are “no different from a terminally ill person (...) that you have to care for until the end, with everything you can.” A more widely shared argument to object to surplus embryo research, however, was the thought that “there is a very clear price for ‘manufacturability’”, and that we should steer clear from attempts “to play God and [make things] better and more perfect but [only] to our [own] advantage, not [to the advantage] of the whole picture, so to speak”, which would include accepting life’s imperfections, such as infertility.

The proposal with research embryos sparked debate across all groups. In the focus group with professionals, the main issue of discussion was under what conditions it could be justified to create embryos for research. Prominent considerations were *the aims of research*, which had to be “very important”, and *the alternatives available*, given that research with research embryos should only be considered if its aims “cannot be obtained in any other [morally less controversial] way”, including the use of surplus embryos. Even so, one of the professionals struggled with the acceptability of creating embryos for research: “as an academic, I’d say yes, actually it should be possible, for example, for the improvement of IVF. But if I look at my ranking [in the previous exercise], then it actually doesn’t feel quite right.” Lay participants were also visibly more uncomfortable with this proposal than with the previous one. Whereas some argued that “whether they’re surplus embryos or whether you [specially] create them yourself, comes down to nearly the same thing”, most agreed that there is still an important difference. As summarized by one of these participants:

“I wouldn’t agree [with this proposal]. I feel like [surplus] embryos were created for IVF, so those were already made in case [the IVF-treatment] didn’t work (...). [But] when [embryos] are specially created, [they are] created to be killed. And I don’t know, I think (...) that’s the difference for me. They are made for a different purpose.”

For several participants, this difference was big enough to object to the creation of research embryos. Others felt that certain research aims may still be important enough to justify it if, “with the results of that research, you [could] help people [more] than you could inflict harm on those embryos”.

The participants’ views on the permissibility of research with hELS depended on the features hELS possessed, among which most prominently those associated with the capacity toward further human development and the capacity to feel. Lack of developmental potential, for instance, was generally taken to mean that research with hELS should be given precedence over research with embryos. After all, a professional stated, “the attractive thing about [hELS] seems to be that (...) they don’t have that potential at all.” But once hELS were conceived to have that potential, views diverged. For one of the lay participants, for instance, if hELS had a potential toward further human development, research with them would be tantamount to research with embryos and, on this participant’s view, impermissible. Others agreed that if hELS were to have a developmental potential akin to embryos, their research use would indeed become more contentious, but for different reasons. One of the professionals, for example, preferred that research were conducted with research embryos over (viable) hELS due to the concern that the latter may open opportunities for misuse, such as the possibility “to create clones.” This prompted a fellow professional to argue that even if hELS were to have the developmental potential of embryos, there would still be good reasons to prioritize their research use:

“Look, if you can just create [hELS] from a little bit of material you already have, then you don’t have to ask me which has my preference. If the risks and the moral protection [that should be afforded] are the same (...) I still think preference should be given to [hELS] because you do not need oocyte donors [to create them].”

Another reason to prefer research with hELS over human embryos—even if both were conceived to be viable—was their ‘artificial’ origin. This reasoning was especially perceptible in lay groups, with several participants arguing that they intuitively felt hELS were due less protection than embryos precisely because

they are merely “put together”, “artificial” or “something out of a lab”, meaning that their research use could thus be “subservient to what we want to know and what we can do with it”.

For several—though again especially lay—participants, these considerations implied that research with hELS should be allowed until stages preceding the development of the organismal features they thought were morally relevant, among which most prominently those associated with sentience. In one of the lay groups, for example, this was taken to mean that research with hELS could continue “up to a few weeks. (...) Well, what had we just said (...)? Four weeks? Eight weeks? [Up to the development of] the nervous system, [up to] that [point]”. Another feature was a beating human heart:

“Well, if it is an embryo-like structure, [and] if it is not the case that the heart starts beating on the 22nd day, then you can do research for a longer [period of time]. (...) But the moment the heart develops, I say ‘until here and no further’.”

Individual interviews

Notably, all five interviewees were hesitant about human embryo research. For those reasoning from religious worldviews, this had to do with the embryo’s moral status. This was especially clear in the interviews with Catholic and Protestant interviewees, according to whom it is because human embryos are due *full moral status from conception* that they should never be treated *as mere means*, but always also as *ends in themselves*. This meant that research with both surplus and research embryos is categorically wrong. As the Protestant interviewee explained, the morally right approach would be to create no more embryos than can be transferred in one IVF-treatment cycle. Since that is not how IVF is normally done, this interviewee felt that the best thing to do with surplus human embryos would be to “either offer them for adoption by couples who cannot generate embryos of their own, or just let them die. (...) If there is nothing you can do for a human being, you let it die. But you’re not going to use it as experimental material, [just like you would] not use someone who is dying as experimental material.”

The interviewees reasoning from Jewish and Islamic perspectives were not thrilled about surplus embryo research either, but they did consider it justifiable under certain conditions. This more liberal stance was based on the relatively low moral status that these perspectives confer to human embryos at stages preceding ensoulment—and the even lower status they confer to embryos *ex utero*. In particular, it was because of this relatively low status, combined with the utility that surplus embryo research could have for IVF or other medically important purposes, that the proposal was considered proportional. The creation of embryos for strictly instrumental purposes was considered by both interviewees as illegitimate, however. As explained by the interviewee reasoning from an Islamic perspective, the problem here is not that “...you’re killing someone (...). The specially created embryo does not have the moral status of a human being. But it does have a status—a moral status—that must be respected.”

The interviewee reasoning from a Humanist worldview was also clearly hesitant about research with both embryos and hELS, albeit for very different reasons. Here, the predominant concern was that we might not be wise enough to deal with the powerful knowledge that this type of research could provide. For research with hELS particularly, this concern became especially pressing if imagined to be used reproductively and in combination with other recent technological advancements—such as CRISPR-Cas technology:

“I do not mean to say that there can never be a good reason to do this [type of research] anyway. (...) But I have the strong feeling that we have to be very cautious [not] to build too much knowledge on this area because we’re also building artificial wombs, we are also building ever more accurate gene [editing] tools... We are working with so much information and genetic technology that, at some point, we really do have a Brave New World.”

By contrast, interviewees reasoning from Catholic, Protestant, and Jewish worldviews were notably receptive of research with hELS as long as they do not have the (‘active’) potential of human embryos. In that case, hELS were conferred at most *extrinsic* moral value and their research use was considered acceptable even beyond the emergence of—what several focus group participants considered—morally relevant features (e.g., heartbeat or early brain development), which, for these interviewees, only mattered *intrinsically* if they indicated ‘a human being in embodiment’. Although the interviewee reasoning from an Islamic perspective agreed that research with hELS that lack developmental potential would raise fewer ethical challenges than research with human embryos, it was also noted that they would still have “a special value because [the stem cells from which they are created] come from a human being. (...) So, if embryo-like structures arise from human material, then they are important.”

Discussion

In the first theme, consensus was found in the view that appropriate terminology for (specific types of) hELS should provide a shorthand for their (dis)similarity to human embryos. The contrast in the adjectives participants used to distinguish between hELS and embryos—e.g., ‘artificial’, ‘synthetic’, or ‘embryo-like’ structures versus ‘real’, ‘natural’, or ‘actual’ embryos—suggests as much. The problem was reaching an agreement on the terms that could reflect this (dis)similarity effectively. For instance, whereas certain terms (e.g., ‘synthetic’) were perceived as inadequate for having normative connotations that could prematurely define the scope of public debate, others (e.g., ‘embryo-like’) were perceived as being so vague that they would prevent the ability to form a normative opinion altogether. These results suggest that too abstract terminology may indeed have little (or: too much) meaning to non-scientists (Sturmey, 2021), which echoes the growing scholarly emphasis on improving naming conventions for hELS (Matthews et al., 2021; Rossant and Tam, 2021). Prompting these issues, however, were more fundamental questions about the criteria upon which embryo definitions should be based. Prominent candidates were ‘fertilization’ and ‘a potential to develop into a human being’. The fact that these questions arose not only in view of hELS but also in view of human embryos corroborates the agenda-setting input previously set forth with regard to the indeterminacy of traditional embryo definitions and the urgency to reconsider those (Pereira Daoud et al., 2020).

The second theme consisted of two exercises, both of which were intended to understand how our participants thought about the protection that should be afforded to hELS. The first exercise asked participants to rank organisms of different kinds in order of importance. For the focus group participants and interviewee reasoning from a non-religious worldview this exercise was not easy. For most lay participants, it was not even something they had thought about before. It is therefore noteworthy that their rankings and considerations were very similar to those of the participants in the focus group with professionals, for whom at least the ethics of human embryo research was familiar territory. In these groups, non-human beings were generally ranked below human beings—at least, below human individuals that have been

(the adult and child) or technically could be (the 24-week-old foetus) born. Although a few lay participants relied on an unvarnished ‘specieist’ reasoning, most others sought morally more substantive reasons for conferring greater protection to these over other organisms. Two chief considerations were: (1) ‘are these organisms capable of feeling pain?’, and (2) ‘are these organisms capable of more complex forms of self-awareness?’

Considerations of this kind are prominent in traditional ethical debates about moral status, and map especially well onto the distinction McMahan draws between *the morality of interests* and *the morality of respect* (McMahan, 2002). Essentially, while *the morality of interests* applies to any being whose interests can be thwarted (among which non-human organisms), *the morality of respect* applies only to *persons*, i.e., beings “on an equal footing with ourselves” (McMahan, 2002). Although personhood is too philosophically complex to discuss in depth here (Goodman, 1998), it is commonly associated with more sophisticated capacities, such as “moral agency, autonomy, the capacity for intentional action, rationality, self-awareness, sociability, and linguistic ability” (DeGrazia, 2008). It is by virtue of these capacities that persons command respect, and it is by virtue of that respect that they should never be treated as mere means (instrumentalised), but always as ends in themselves. Organisms that fall below what McMahan refers to as ‘the person threshold’, however, may be justifiably used instrumentally, albeit under conditions of proportionality and subsidiarity (Jans et al., 2018).

The (relatively low) protection many afforded to early forms of human life—i.e., the embryo, zygote and hELS—seemed to stem exclusively from considerations pertaining to *the morality of interests*. To these participants, the greater protection afforded to embryos than to zygotes was explicitly grounded in the idea that whereas embryos can be sentient, and thus have some interests that can be thwarted, zygotes certainly cannot. The same reasoning often also applied to hELS. If participants assumed hELS were incapable of feeling pain, most placed them at the bottom of their rankings. But as the second exercise later clarified, in the—admittedly very unlikely—event that hELS could become sentient, participants would confer them (much) greater protection from then on. Sometimes, a protection high enough to halt their use in research even if they clearly lacked any real developmental potential. For these participants, as well as for the interviewee reasoning from a non-religious worldview, considerations pertaining to *the morality of respect* were thus apparently not viewed as providing a suitable basis for protecting early (forms of) human life. Here, the underlying idea presumably is that the capacities associated with personhood cannot yet exist at these early stages, and that the protection afforded to zygotes, hELS, embryos, and even more fully developed foetuses, cannot stem from the respect due to persons. Hence, the only kind of considerations that could matter for these organisms’ (intrinsic) moral status are those pertaining to *the morality of interests*.

At the same time, several other focus group participants and all individual interviewees reasoning from religious worldviews placed early forms of human life very high in—or even at the very top of—their rankings. These rankings were based on ‘arguments from potential’, according to which early human beings are *potential persons*, if not *persons with potential*. As McMahan explains, to argue that early forms of human life are *potential persons* is basically to say that personhood is “a phase sortal—that is, a predicate that may apply to us only during a certain phase, or certain phases, of our existence” (McMahan, 2002). By contrast, to argue that early forms of human life are *persons with potential*, is to argue that all human beings are essentially persons, even if their personhood is only “latently or even occultly present” (McMahan, 2002). Those who placed forms of human life between high and middle-high positions but nevertheless

discerned between the protection afforded to organisms at different stages, seemed to hold the view of *potential persons*. On this view, both the continuity (i.e., the developing entity is predisposed to become a person) and the discontinuity (i.e., the developing entity is not a person yet) matter morally. On the one hand, the fact that early forms of human life are not yet persons implies that *the morality of respect* cannot yet apply to them. On the other hand, the fact that they—unlike other (non-human) organisms—have a predisposition toward personhood provides an additional reason to protect them. The gradually increasing degree of protection these participants afforded to developing human beings at different developmental stages—conferring greater protection to fetuses than to embryos, and greater protection to embryos than to zygotes, even though all three are ‘potential persons’—aligns well with this reading of potentiality. By contrast, those who placed all forms of human life at the top of their rankings without differentiating between them, seemingly view early human organisms as *persons with potential*. In this reading, personhood is an uninterrupted continuum: early forms of human life *are essentially persons*—albeit ‘incomplete’ ones, or persons in the process of becoming—and therefore stand ‘on an equal moral footing with ourselves’. On these participants’ view, it thus makes little sense to distinguish between the degrees of protection afforded to embryos and fetuses: both *already are persons* and therefore due *equal respect*. This reading was echoed by a (small) number of focus group participants, but much more pronounced in interviews with respondents reasoning from religious worldviews, which confirmed what we already knew about the moral status due human beings (with potential) on these views (Walters, 2004; Schenker, 2005; Kerridge et al., 2010; Neaves, 2017). Whereas the interviewees reasoning from Christian worldviews argued that it cannot be ruled out that personhood begins at conception, and therefore assumed the precautionary stance that *the morality of respect* would also apply to zygotes, the interviewees reasoning from a Jewish and Islamic perspective argued it begins at later stages (starting from the ensoulment, at day 40 and 120 in development, respectively), meaning that *the morality of respect* can only apply to human organisms past those stages.

Regardless of one’s reading of personhood, the (gradually increasing or full) protection participants’ conferred human embryos based on their potential to become (or develop as) persons, would only extend to hELS if they too have that potential. For this potential to matter intrinsically, it must involve more than mere possibility. It must involve what the ethical literature denotes as ‘active potentiality’, i.e., an *inherent* and *autonomously driven* predisposition toward personhood (Buckle, 1990; Reichlin, 1997; Denker, 2006, 2021). The suggestion that any uncertainty about hELS acquiring such a potential could be avoided by building in ‘suicide genes’ is reminiscent of the earlier proposal for ‘altered nuclear transfer’ as a supposedly morally non-problematic approach to creating a source for patient-specific human embryonic stem cells (hESCs). This proposal involved combining so-called ‘therapeutic cloning’ with a genetically engineered defect meant to ensure that the resulting ‘entity’ would be unable to implant and, therefore, lack the potential to grow into a human being (Hurlbut, 2005). When this idea was discussed in the United States’ President’s Council on Bioethics (2004), Doerflinger, the secretary of the American bishops’ conference, proved not to be convinced by this strategy for the same reason brought up by some of our religious interviewees: for Doerflinger, the fate of human embryos that would have been modified to stagnate development after a certain stage was comparable with the limited life-expectancy of persons known to be carrier of Huntington’s disease. A further interesting observation from our results is that, for some participants, the ‘artificiality’ of hELS was taken to imply that

these structures could not have the ‘active’ potential of human embryos—even if they too could produce a human being—and therefore reason to protect them less than human embryos at similar stages. This view was explicitly advocated by the interviewee reasoning from an Islamic worldview, for example. According to this interviewee, even if hELS had the potential to produce a human being, this potential would still be the result of external manipulation, rather than the result of an intrinsic and autonomously driven predisposition. That viewing the potential of (artificial) hELS as qualitatively different from the potential of (non-artificial) human embryos may lead to disturbing and far-reaching implications also became apparent, however. The lay participant according to whom any individual resulting from the (hypothetical) reproductive use of hELS would ‘not be a real human being’ for a lack of a unique DNA, for instance, showed how this perspective may have moral implications beyond the context of research. Clearly, it would be troubling to consider human clones (and indeed: identical twins) as having less moral status than other human beings.

The second exercise probed the participants’ views on the acceptability of research with hELS specifically by comparing hypothetical research scenarios with surplus embryos, research embryos, and hELS, respectively. These views were again noticeably in line with those taken in scholarly debates about the ‘discarded-created’ distinction (Macklin, 2000; Steinbock, 2020; Devolder, 2004, 2012, 2013; de Miguel-Beriaín, 2014) and the ‘14-day rule’ (Cavaliere, 2017; Hurlbut et al., 2017; Appleby and Bredenoord, 2018; Williams and Johnson, 2020; Peters, 2021; Hyun et al., 2021; Nicolas et al., 2021).

Our participants’ views suggest that these rules need not extend to hELS that lack the ‘active’ potential of human embryos—which incidentally may also have implications for non-viable human embryos (Pereira Daoud et al., 2020). As previously discussed, if there is no real capacity to become persons, only considerations arising from *the morality of interests* can matter. Hence, only if these hELS were sentient, for example, would there thus be reason to restrict their research use. While most participants seemed to think of sentience as a hard research limit, it is not evident that this needs to be the case. As previously mentioned, actions that cause pain or discomfort can still be justifiable from the perspective of *the morality of interests*, albeit under conditions of proportionality and subsidiarity. This is not to say that hELS that lack potential are completely innocuous, however. Even though most participants indeed welcomed research with (non-viable) hELS as a morally preferable alternative to research with (viable) human embryos, a few of them still raised issues they believed warrant consideration. Even though most of these issues were not new, the fact that a beating heart was also mentioned as a morally relevant limit for research with hELS is an interesting finding due to a lack of theoretical grounding. In the ethical literature, a heartbeat is usually only considered to grant (symbolic) moral value if it represents ‘a human individual in the process of becoming’ (Aach et al., 2017; Hurlbut et al., 2017). But the participants that mentioned this feature viewed it as a categorical limit for research with any hELS—even if they evidently lacked a potential toward human development. Our hypothesis is that these participants must have relied on a reversal of traditional approaches to moral status: instead of the feature (in this case, the heartbeat) deriving its moral significance from the value of the human being it denotes, the human organism (which, in this case, cannot become a human being) is taken to derive its value from that of its feature.

By contrast, if hELS were conceived to have the ‘active’ potential of human embryos, the question arose whether their research use too should be bound by the limitations of the Dutch Embryos Act. Of course, for participants that viewed this as

implying that hELS would be *persons with potential*, any research that would treat them as mere instruments was deemed categorically wrong. But similarly to debates about human embryos, this was only a very small minority. For most participants, even if hELS were *potential persons*, they were not persons *yet* and could therefore be subject to research under considerations of proportionality and subsidiarity. Moreover, there may well be reasons to prefer their research use over that of human embryos even when both have an ‘active’ potential. Prominent reasons were, for example, that hELS do not require gametes, and therefore avoid the scarcity and burdens associated with oocyte donation when compared to research embryos; or that their ‘artificiality’ and the fact that they are specially created to serve as research material would make them more suitable for certain studies when compared to surplus embryos. For these participants, there were thus good reasons to regulate research with hELS differently from research with human embryos. This led to discussions about the current Dutch ban on research embryos, which—if hELS had a potential akin to human embryos—would bar their creation, and the 14-day rule, the reasoning behind which could be easily evaded by the developmental plasticity of hELS.

Limitations and recommendations for further research. This study should of course be understood within the context of its limitations, one being the relatively small number of focus group and individual interviews it consists of, which prevents the generalization of these results to broader publics. Another potential limitation to note is that of selection bias in the pilot focus group and in the focus group and individual interviews with professional participants, all of which were selected by and from the networks of the research team. The same applies to the collection of the results, in which interviewer bias cannot be ruled out, and subsequent analysis, which necessarily involves a certain degree of interpretation and may therefore have been construed differently by different researchers. Finally, although participants were generally informed both prior to (in writing) and during (verbally) the interviews, it can also not be ruled out that certain misunderstandings of the science may have nonetheless remained.

Having that said, our study shows that the arguments participants articulated and the spectrum of positions they took with regard to the conceptual and moral qualification of hELS line up well with the arguments and positions found in the ethical literature. Even though the artificiality of hELS seemed to play a bigger role in lay group discussions, no other significant differences were found between professional and lay perspectives. Lay citizens thus seem quite capable of considering the development of hELS from an ethical perspective, which can hopefully help allay concerns about lay publics not being able to meaningfully participate in debates about the ethical ramifications of (novel) scientific developments. The fact that these perspectives also align well with several of the ISSCR’s recently updated guidelines for research with hELS (Lovell-Badge, 2021; Lovell-Badge et al., 2021; ISSCR, 2021) further supports this thesis. The guidelines were unfortunately only updated after we had collected the data and could therefore not be taken on board during the interviews. But the participants’ emphasis on tying research limits into particular ethical considerations, rather than into time in culture, maps nonetheless well onto the thrust of these recommendations (ISSCR, 2021). Another example can be found in the participants’ greater preoccupation with ‘viable’ hELS, which corresponds with the ISSCR’s advice to review research with so-called ‘integrated’ models—i.e., hELS that could come to have a developmental potential akin to human embryos—more stringently.

This is not to say that possessing ‘a potential for further human development’ was decisive in distinguishing between contentious from non-contentious research. Research with hELS that were conceived to be evidently incapable of developing into human beings—called ‘non-integrated’ models by the ISSCR—also raised moral concerns in focus group discussions, for instance. These concerns were primarily linked to neural and brain development, which participants worried could make these structures sentient (albeit only in a very rudimentary sense). Whether and from whence this could be possible, as well as what that would imply for the acceptability of their research use, remains of course to be established. The alleged moral relevance of a heartbeat in entities that cannot grow into human beings is another issue that those involved in the development of guidelines for research with hELS may wish to further explore and connect with. But ‘potential’ clearly also need not provide a categorical moral basis for cutting-off research. Here, questions emerge about what we exactly mean when talking about ‘potential’ and what that does or does not imply for research with hELS that could come to possess it; an issue we—and hopefully others—will take up for further analysis.

Data availability

The datasets generated from the focus groups with lay citizens are stored in DataVerseNL, <https://doi.org/10.34894/UFM8MN>. The datasets generated from individual interviews and the focus group with professionals are not publicly available due to risk of identification but are available from the corresponding author on reasonable request.

Received: 18 January 2022; Accepted: 14 April 2022;

Published online: 28 April 2022

Notes

- 1 The two remnant themes are reported in a separate manuscript.
- 2 Note that the Dutch Embryos Act presently prohibits the creation of human embryos for research purposes. At the same time, the ban is also the subject of current societal debate. For the purpose of our study, participants were therefore asked to imagine a scenario in which, as a result of this societal debate, the ban would have been lifted and research with ‘research (human) embryos’ would have been legally allowed under certain conditions (see Supplementary Information).

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Acknowledgements

We are grateful to all participants for their insightful contributions to our study.

Competing interests

ALB is a member of the ISSCR Ethics Committee, the IQVIA’s Ethics Advisory Panel and the Dutch Senate. AMPD, WJD and GMWRdW have no relevant financial or non-financial interests to disclose.

Ethics approval

The Research Ethics Committee (REC) of the Faculty of Health, Medicine and Life Sciences of Maastricht University determined that this study was exempt from the Medical Research Involving Humans Act (WMO) and recommended that the Dean, on behalf of the Board, formally approved of the study (ethics approval number: FHML-REC/2020/018). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent

By signing the written informed consent form, participants consented to the publishing of their de-identified data.

Additional information

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