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# Broad support for regulating the clinical implementation of future reproductive techniques

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**STUDY QUESTION:** Do gynaecologists, infertile patients and the general public, consider that regulation of the clinical implementation of stem cell-based fertility treatments is required?

**SUMMARY ANSWER:** There is broad support from gynaecologists, patients and the general public for regulating the clinical implementation of future stem cell-based fertility treatments.

**WHAT IS KNOWN ALREADY:** There is debate on the need to regulate the clinical implementation of novel techniques. Regulation may hinder their swift adoption and delay benefits for patients, but may prevent the implementation of ineffective or harmful techniques. Stem cell-based fertility treatments, which involve creating oocytes or spermatozoa by manipulating stem cells, are likely to be implemented in clinical practice in the near future and will probably impact future generations as well as the current one.

**STUDY DESIGN, SIZE, DURATION:** A cross-sectional survey was conducted among gynaecologists working in fertility clinics ( $n = 179$ ), patients with severe infertility ( $n = 348$ ) and a representative sample of the general public ( $n = 1250$ ). The questionnaire was disseminated in the Netherlands in the winter of 2015–2016.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** The newly developed questionnaire was reviewed by experts and tested among the general public. The questionnaire assessed whether participants wanted each of nine potential negative consequences of the clinical implementation of stem cell-based fertility treatments to be regulated. In addition, the importance of all negative and positive potential consequences, the appropriate regulatory body and its need to consult with advisors from various backgrounds was questioned.

**MAIN RESULTS AND THE ROLE OF CHANCE:** In total, 958 respondents completed the questionnaire (response rate: 54%). A large majority of each participant group (>85%) wanted regulation, for at least one potential negative consequence of the clinical implementation of stem cell-based fertility treatments. The majority of all participant groups wanted regulation for serious health risks for intended parents, serious health risks for children and the disposal of human embryos. Regulation for out-of-pocket costs and the burden of treatment received little support. The majority of gynaecologists and the general public, but not the patients, requested regulation for the risk of minor congenital abnormalities, the success rates and the naturalness of treatments. Nevertheless, the majority of patients did consider the former two potential negative consequences important. The majority of all groups preferred a national bioethics committee as the regulatory body. This committee should consult with advisors from various backgrounds and should consider the broader context of potential consequences of the stem cell-based fertility treatments.

**LIMITATIONS, REASONS FOR CAUTION:** This empirical study focuses on only three stakeholder groups. This study reports on the perspective of the majority and this is not per definition the morally right perspective. The transferability of our findings to other cultures and other techniques remains unclear.

**WIDER IMPLICATIONS OF THE FINDINGS:** A national bioethics committee, consulting with advisors from various backgrounds, should regulate the clinical implementation of future stem cell-based fertility treatments. Whether this broad support for regulation applies to novel techniques from other fields of medicine should be examined.

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**Key words:** reproductive techniques / social control, formal / social control, informal / health care quality, access and evaluation / investigative techniques / stem cells / reproductive medicine / delivery of health care / public opinion / attitude

## Introduction

The progress of medicine results in the continuous development of novel techniques.

Whereas some novel techniques are adjuncts or 'add-ons' for treatments performed daily in clinical practice (e.g. embryo glue for IVF), others differ substantially from treatments performed daily in clinical practice (e.g. stem cell-based fertility treatments, which involve creating oocytes or sperm by manipulating stem cells) (Hendriks et al., 2015a; Harper et al., 2017). The speed at which some novel techniques progress from development to widespread clinical implementation, without sufficiently considering their clinical and societal consequences, led to a debate about the need for regulating the clinical implementation of novel techniques (Spodick, 1975; Grimes, 1993; Margo, 2001; Schatten, 2002; Lindvall and Hyun, 2009; Dondorp and de Wert, 2011; Harper et al., 2012, 2017; ASRM, 2015; Strasberg and Ludbrook, 2003; Wilson, 2006). The debate hinges on whether demanding reassuring outcomes from time and resource consuming clinical trials in order to implement novel techniques is beneficial for patients' well-being (Spodick, 1975; Grimes, 1993; Margo, 2001; Schatten, 2002; Lindvall and Hyun, 2009; Dondorp and de Wert, 2011; Harper et al., 2012; ASRM, 2015; Charo, 2015; Strasberg and Ludbrook, 2003; Wilson, 2006). On the one hand, regulation may hinder the development and swift widespread adoption of novel techniques that turn out to benefit patients. On the other hand, regulation can prevent premature implementation of novel techniques that turn out to be ineffective or even harmful for patients.

Many professionals are pleading for regulation for the clinical implementation of novel techniques (Grimes, 1993; Margo, 2001; Schatten, 2002; Lindvall and Hyun, 2009; Dondorp and de Wert, 2011; Charo, 2015; Strasberg and Ludbrook, 2003). Multiple stakeholder groups should be involved in this discussion (Blank, 1990). Patients are important stakeholders as they face the consequences of their disease and its treatment. Medical doctors are also pivotal as they decide on a day-to-day basis which treatments to offer their patients (Johnson, 2001). Finally, members of the general public should be involved since these novel techniques have broader societal and ethical consequences (Blank, 1990; Charles and DeMaio, 1993; Litva et al., 2002; Furger and Fukuyama, 2007; Martin et al., 2002; Martin, 2008). So far, insight into the support from these three stakeholder groups for regulating the clinical implementation of novel techniques is missing. In addition, it is unclear whether stakeholders consider the government, an association of physicians, or a national bioethics committee as the most appropriate regulatory body (Blank, 1990; Johnson, 2001; Massarani and de Castro Moreira, 2005; Furger and Fukuyama, 2007; Strasberg and Ludbrook, 2003). Whether the regulatory body should consult with advisors from different backgrounds while setting up their

regulation has not been assessed systematically (Stronks et al., 1997; Singer et al., 2000; Martin et al., 2002).

Responsible implementation of novel techniques is especially important for reproductive medicine, which not only affects the patients involved but also affects future generations. Numerous fertility treatments, including pre-implantation genetic screening and intra-cytoplasmic sperm injection have been rapidly introduced into clinical practice (Dondorp and de Wert, 2011; Harper et al., 2012). Currently, stem cell-based fertility treatments are being developed in animal models (Hendriks et al., 2015a,b; Boiani, 2017; Cohen et al., 2017). The nine types of stem cell-based fertility treatments mainly differ in two respects (Hendriks et al., 2015a,b). Firstly, they can start from germline stem cells obtained by a testicular biopsy (i.e. spermatogonial stem cells; not possible for all intended parents) or from somatic cells which are induced to become pluripotent stem cells (in theory possible for all intended parents). Secondly, the stem cells can differentiate into spermatozoa or oocytes in vitro or in vivo after transplantation into the patient's testes or ovary (Hendriks et al., 2015a,b). Recent opinion papers have called for responsible clinical implementation, as stem cell-based fertility treatments have been flagged as a potentially disruptive novel technique with significant clinical and societal consequences (Hendriks et al., 2015a,b; Cohen et al., 2017). More specifically, stem cell-based fertility treatments may have unpredictable health effects on future generations and may fundamentally change reproduction by enabling all individuals to attempt to achieve genetic parenthood (with a gestational carrier if need be) irrespective of their fertility problem, relational status or sexual orientation.

We aimed to study whether gynaecologists, infertile patients and the general public consider that regulating the clinical implementation of future stem cell-based fertility treatments is required.

## Materials and Methods

A cross-sectional survey was conducted in the Netherlands from November 2015 to February 2016 amongst gynaecologists, patients with severe infertility and members of the general public.

### The questionnaire

A questionnaire with five parts was developed (Supplementary Material). Part I asked about demographic background. Part II informed participants about future stem cell-based fertility treatments to enable them to make an informed opinion. It also explained that these treatments were not yet available. Part III detailed 14 potential positive consequences (e.g. curing infertility) and 18 potential negative consequences (e.g. risk of major abnormalities) of future stem cell-based fertility treatments, in lay language and questioned their importance with a 4-point Likert scale. This triggered participants to actively consider all potential consequences rather than only passively reading about them. These consequences were identified by

literature review and qualitative interviews with patients and gynaecologists (Hendriks *et al.*, 2014, 2015a,b, 2017b). Part IV focused on the nine negative consequences, which are most susceptible to regulation and included: the risk of major congenital abnormalities, the risk of minor congenital abnormalities, the risk that the resulting child develops a chronic disease, the risk that the intended parent develops cancer, success rates, out-of-pocket costs, the disposal of human embryos, the burden of treatment and the 'naturalness' of the treatment. For each one of these nine negative consequences, participants were asked whether the decision about their acceptability should be taken by the individual patients and their gynaecologists, or by regulatory bodies such as a national bioethics committee, or a professional association of gynaecologists, or the government. In addition, part IV questioned the need for the regulatory body to consult with 10 advisors from various backgrounds (e.g. scientists, religious representatives) before making a decision. The questionnaire was disseminated together with another questionnaire (Hendriks *et al.*, 2017a,b) and the package ended by giving participants the opportunity to give 'any additional comments in relation to these questionnaires'.

The questionnaire was assessed and adjusted by 10 independent experts in communication, political science, sociology, ethics, law, medicine and biology as well as patient-representatives in order to safeguard its completeness and non-directive phrasing (Molewijk *et al.*, 2003). The questionnaire was then pilot tested and adapted for feasibility during cognitive interviews with 18 members of the general public (number defined by data-saturation) (Willis, 2004).

## Data collection

The questionnaire was disseminated together with a questionnaire for another study which examined the acceptability of stem cell-based fertility treatments for different indications (e.g. same-sex couples) (Hendriks *et al.*, 2017a,b). The recruiting clinic's ethics committee confirmed no ethics approval was needed (W15\_191).

All 179 gynaecologists working in a Dutch fertility clinic received an invitation letter, a coded questionnaire, a refusal form and a return envelope by post. Non-responders received two reminders by email including a link to an online version of the questionnaire.

In addition, we contacted both partners of 174 heterosexual couples diagnosed with severe male or female infertility in the Academic Medical Center of Amsterdam between August 2012 and November 2015. Couples who had non-obstructive azoospermia and no sperm in their testicular biopsy ( $n = 119$  couples) or those with poor ovarian response (i.e. defined as the retrieval of  $\leq 3$  oocytes or cycle cancellation in at least two IVF-cycles with controlled ovarian stimulation using at least 225 IU of gonadotropins (Ferraretti *et al.*, 2011);  $n = 55$  couples) were eligible. These patient groups were selected as they are likely to be the first to whom stem cell-based fertility treatments will be offered. Eligible couples received an invitation letter, two coded questionnaires (one per partner), a refusal form and a return envelope via postal mail. Non-responders received two reminders.

Finally, a sample of 1250 members of the general public, matching the demographic characteristics (i.e. sex, age, education, household size, region) of the Dutch adult population, was drawn from an actively recruited panel of a certified research company (i.e. TNS-Nipo). The questionnaire for the general public was disseminated online and no reminders were sent.

## Outcomes

The proportion of participants per group (i.e. gynaecologists, patients and the general public) who considered that regulation is required for at least one of the nine potential negative consequence of stem cell-based fertility treatments susceptible to regulation was reported. In addition the following was noted, for each group of participants: (i) the proportion requesting regulation of each of the nine potential negative consequences, (ii) the

proportion (only of the participants requesting regulation) selecting each of the proposed regulatory bodies as most appropriate and (iii) the proportion requiring the regulatory body to consult with three or more of 10 proposed advisors from different backgrounds, and the proportion per advisor, (iv) the proportion considering it 'important' or 'of the utmost importance' that the regulatory body takes account of each of the 18 negative and 14 positive potential consequences of the clinical implementation of stem cell-based fertility treatment.

## Statistical analysis

Chi-square tests compared the three groups of participants with respect to their likeliness to deem that regulation is required for at least one of the nine potential negative consequences susceptible to regulation and for each of them. Per group of participants, the most appropriate regulatory body for each of the nine negative consequences (according to the participants deeming regulation required) were pooled. Chi-square tests compared the three groups with respect to the proportions of participants selecting each of the regulatory bodies. Significant Chi-square tests were followed up with post hoc Bonferroni corrected pair-wise comparisons.

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## Results

The questionnaire was filled out by 958 participants (response rate, RR = 54%), including: 82 gynaecologists working in fertility clinics (RR = 46%), 104 patients with severe infertility (RR = 30%) and 772 members of the general public (RR = 62%). Table I presents the demographic characteristics per group. The general public represented the Dutch adult population regarding several demographic characteristics (i.e. gender, age, education, household size and region).

### The need for regulation

A large majority (>85%) of all three participant groups considered that regulation is required for at least one of the nine potential negative consequences (Table II). The three participant groups did not differ significantly in this respect ( $P = 0.09$ ).

The majority of all participant groups considered that regulation is required for four of the nine potential negative consequences. The four were; the risk of major congenital abnormalities, the risk that the child would develop a chronic disease, the disposal of human embryos and the risk that the intended parent would develop cancer. The exact size of the majority differed between groups ( $P < 0.01$ ) as displayed in Table II, except for the disposal of human embryos ( $P = 0.41$ ).

Rather than requesting regulation, the majority of all participant groups agreed that individual patients and their gynaecologists could decide on the acceptability of out-of-pocket costs and the burden of these future treatments. Again, the exact size of the majority per group differed ( $P < 0.001$ ) as displayed in Table II.

For the remaining three potential, negative consequences, the majority of both gynaecologists and the general public was in favor of regulation and the majority of patients thought individual patients and their gynaecologists could make the decision. More specifically, this included the risk of minor congenital abnormalities ( $P < 0.001$ ), the naturalness of treatments ( $P < 0.001$ ) and their success rates ( $P < 0.001$ ).

**Table 1** Demographic characteristics of participants in the survey.

Participant characteristics	Proportion (%) by participant group		
	Gynaecologists	Patients	General public
Gender			
Male	42/82 (51)	50/104 (48)	383/772 (50)
Age (y)			
18–43	21/81 (26)	94/104 (90)	316/772 (41)
43–65	55/81 (68)	10/104 (10)	302/772 (39)
>65	5/81 (6)	0/104 (0)	154/772 (20)
University degree	82/82 (100)	60/104 (56)	218/771 (28)
European ethnic background	75/82 (92)	87/103 (85)	718/772 (93)
Religion			
Christian	43/77 (56)	26/78 (33)	362/724 (50)
Atheist or agnostic	30/77 (39)	34/78 (43)	301/724 (42)
Other, including Muslim, Jewish	4/77 (5)	18/78 (24)	61/724 (8)
Importance of religion <sup>a</sup>	1.8 ± 2.5	2.2 ± 3.1	2.0 ± 3.1
Yearly household income			
Above modal (>€38800)	72/74 (97)	76/94 (81)	332/603 (55)
Social status			
Upper class	82/82 (100)	28/104 (27)	146/772 (19)
Higher middle class	0/82 (0)	54/104 (52)	227/772 (36)
Lower middle, working, or lower class	0/82 (0)	22/104 (21)	349/772 (45)
Political preference: right-left			
Right-wing (1–4)	32/81 (40)	34/98 (35)	249/772 (32)
Moderate (5–6)	18/81 (22)	36/98 (37)	293/772 (38)
Left-wing (7–10)	31/81 (38)	28/98 (29)	230/772 (30)
Political preference: progressive-conservative <sup>b</sup>			
Conservative (1–4)	9/80 (11)	15/96 (16)	197/772 (26)
Moderate (5–6)	21/80 (26)	46/96 (48)	286/772 (37)
Progressive (7–10)	50/80 (63)	35/96 (36)	289/772 (37)
In committed relationship	74/81 (91)	104/104 (100)	570/772 (74)
Sexual orientation			
Heterosexual	76/81 (94)	104/104 (100)	703/734 (96)
Sought medical advice for subfertility	6/80 (8)	104/104 (100)	119/772 (15)
Have children	76/81 (94)	26/99 (26)	474/772 (62)
Duration of wish for a child in years	N.A.	4 ± 3	N.A.

<sup>a</sup>Mean ± SD; 0 = not important, 10 = of the utmost importance.

<sup>b</sup>The following explanation was given in the questionnaire: Conservative (preserving societal values), progressive (extending personal freedoms), N.A. = not applicable.

## Appropriate regulatory body

Among those who considered that regulation is required, the most frequently selected regulatory body of choice in all three participant groups, was a national bioethics committee. The responses did differ between the groups ( $P < 0.001$ ) as displayed in Table III.

## Decision-making process of the regulatory body

The majority from each participant group wanted the regulatory body to consult with advisors from at least three different backgrounds (Table III). The (differences in) advisors appointed by each participant group are displayed in Supplementary Table SI. The majority of all

three participant groups supported consulting bioethicists and gynaecologists. Psychologists and/or patients were appointed as advisors by the majority of gynaecologists and patients. The majority of all participant groups valued the regulatory body taking account of 10/14 positive and 10/18 negative potential consequences of stem cell-based fertility treatments (Supplementary Table SII).

## Discussion

There is broad support from gynaecologists, patients and the general public to create a national bioethics committee to regulate the clinical implementation of future stem cell-based fertility treatments. The majority of all three stakeholder groups wants to regulate, the risk of

**Table II** The proportion of participants who believed that regulation was required for each of the nine negative consequences.

Negative consequence	Proportion (%) by participant group deeming regulation required			P-value for difference between participant groups
	Gynaecologists (n = 76)	Patients (n = 101)	General public (n = 772)	
Risk of major congenital abnormality	67/73 (92)	87/100 (87)	603/772 (78)	0.004 <sup>a</sup>
Risk the resulting child develops a chronic disease	65/72 (90)	85/100 (85)	564/772 (73)	<0.001 <sup>a,b</sup>
Disposal of human embryos	50/75 (67)	67/99 (68)	558/772 (72)	0.41
Risk the intended parent develops cancer	62/73 (85)	59/100 (59)	508/772 (66)	0.001 <sup>a,c</sup>
Risk of minor congenital abnormality	56/76 (74)	42/100 (42)	523/772 (68)	<0.001 <sup>b,c</sup>
Unnaturalness	46/76 (61)	32/100 (32)	428/772 (55)	<0.001 <sup>b,c</sup>
Low success rates	59/74 (80)	28/100 (28)	412/772 (53)	<0.001 <sup>a,b,c</sup>
High 'out of pocket' costs	37/75 (49)	21/101 (21)	367/772 (48)	<0.001 <sup>b,c</sup>
Burdensome treatment	33/75 (44)	14/101 (14)	344/772 (45)	<0.001 <sup>b,c</sup>
<b>Total: regulation of at least one of the nine negative consequences</b>	<b>70/75 (93)</b>	<b>91/100 (91)</b>	<b>664/772 (86)</b>	<b>0.09</b>

<sup>a</sup>The general public and gynaecologists differ significantly.

<sup>b</sup>The general public and patients differ significantly.

<sup>c</sup>The gynaecologists and patients differ significantly.

**Table III** The proportion of participants who favored different regulatory bodies and who believed advisors from different backgrounds should be consulted

	Proportion (%) by participant group		
	Gynaecologists	Patients	General public
The most appropriate regulatory body <sup>a,b,c,d</sup>			
A national bioethics committee	247/475 (52)	225/435 (52)	2536/4307 (59)
A medical professional association	143/475 (30)	137/435 (32)	882/4307 (20)
The government	85/475 (18)	73/435 (17)	889/4307 (21)
Advisors from at least three different backgrounds should be consulted <sup>b,c,d</sup>	72/79 (91)	87/102 (85)	479/772 (62)

<sup>a</sup>This is a pooled outcome, based on the responses of participants deeming regulation required for each of the nine consequences (total number of responses from gynaecologists n = 475, from patients n = 435, from the general public n = 4307).

<sup>b</sup>The three groups differed significantly from one another P < 0.001.

<sup>c</sup>The general public and gynaecologists differ significantly.

<sup>d</sup>The general public and patients differ significantly.

cancer for the intended parents, the risk of major congenital abnormalities and chronic diseases in the offspring and the disposal of human embryos. Regulation of out-of-pocket costs and of the burden of treatment received little support. Groups differed in having majority support for the regulatory committee to manage the risk of minor congenital abnormalities and the limited naturalness and success rates of treatments. With regard to the process of setting up regulation, stakeholders want the regulatory committee to consult with different advisors and to take account of the broader context of potential consequences of these techniques.

To the best of our knowledge, this is the first empirical study of stakeholders' perspectives for the need and process of regulating the implementation of a novel technique. Our focus on future stem cell-based fertility treatments (which are still being developed), is timely as it allows reflection prior to actual clinical application rather than a reactive

response post-implementation (Schatten, 2002; Harper *et al.*, 2012). In addition, selecting a reproductive technique is relevant as reproductive techniques affect not only patients but also future generations.

The advantages and disadvantages of several methodological considerations need to be addressed. Firstly, the three stakeholder groups were selected based on their ability to represent society and those taking decisions in clinical practice rather than being selected based on their ability to form a morally sound opinion. Physicians may have a well-intended over-eagerness to treat, a self-interest in offering treatment, and debateable qualifications for deciding on the societal consequences of treatments (Daniels and Taylor, 1993; Furger and Fukuyama, 2007; Harper *et al.*, 2012). As beneficiaries, patients (especially those with severe infertility) may be more willing to take risks and to shift moral boundaries, as their interests (e.g. their reproductive autonomy) are at stake (Johnson, 2001; Shreffler *et al.*, 2010). The

general public may have insufficient knowledge about a disease and its treatment to enable appropriate reflection (Litva et al., 2002). Secondly, it is unclear whether collecting data with questionnaires rather than focus group discussions influenced our findings (Wiseman et al., 2003). On the one hand, focus group discussions give participants more time and peer discussion prior to forming an opinion and allow gathering more in-depth insight, for example on the effect of the (intermediate) cell types used for stem cell-based fertility treatment on the need for regulation. On the other hand, instinctive responses to questionnaires might lead to a more 'valid' representation of societal values and individual consultation reduces susceptibility to normative social influence and prevents groupthink. Thirdly, addressing a sample that is representative for several demographic characteristics of the Dutch population is a methodological strength. Ethnic and religious Dutch minorities were, nevertheless, underrepresented and this limits the transferability of our findings towards other cultures. In addition, the transferability towards future generations might be limited as opinions about novel techniques change over time (Kovacs et al., 2003). Fourthly, for the sake of simplicity our text on the findings describes the perspective of the majority of each stakeholder group but the majority does not by definition have the morally right perspective and the group belief will not be shared by all individuals (Sulmasy and Sugarman, 2001).

Four shortcomings of our study should be mentioned. Firstly, we did not correct for the fact that the participating patients included couples, who might not be considered as independent cases. Secondly, the response rate among patients and gynaecologists was relatively low. This might, in part, be due to the time required for participation as our questionnaire was disseminated together with another questionnaire. It might also be due to the fact that stem cell-based fertility treatments are not yet available and have uncertain potential consequences. We did however attempt to create a feasible questionnaire on a complex decision by breaking it down into specific micro-decisions (Scully et al., 2007). Thirdly, our design did not allow investigating whether our rather concise explanation of stem cell-based fertility treatments (instead of for example detailing cell types used) influenced our findings. The development of our questionnaire focussed on ending up with an explanation understood by people from all (educational) backgrounds, which was unbiased according to an independent expert panel as all negative and positive potential consequences identified by a literature review and qualitative study were mentioned in the beginning of the questionnaire (Molewijk et al., 2003; Hendriks et al., 2015a,b). Fourthly, we selected nine potential negative consequences based on their ease to be regulated, rather than on their importance to stakeholders as we had no information about what the most important consequences were. Our findings on importance presented in Supplementary Table SII show that this resulted in not questioning the need for regulating four potential negative consequences that were important to the majority of all three groups. It is reassuring that the need to regulate the only negative consequence important to the large majority ( $\geq 85\%$ ) of each group was questioned. As an example of the selection made based on the ease to be regulated, it is easier to prevent a large number of disabled children being born by forbidding a therapy with a large risk on major congenital abnormalities, than to prevent the negative consequences of allowing treatment B, by forbidding treatment A which may increase the likelihood of allowing treatment B (i.e. the slippery slope effect).

The identified support from the majority of gynaecologists, patients and the general public for regulating the clinical implementation of future stem cell-based fertility treatments is in line with professionals requesting regulation of the clinical implementation of different kinds of novel reproductive techniques (Schatten, 2002; Dondorp and de Wert, 2011; Charo, 2015; Frith et al., 2011). Of note, this majority support from all three questioned stakeholder groups was not identified for all nine potential negative consequences. Our participants seemed less likely to support regulation of potential negative consequences, which have merely personal implications (i.e. 'out-of-pocket costs' and 'burden'). In contrast to this majority support from the Dutch general public, a study found that only 50% of the UK general public supports involving regulators in case-by-case decisions on mitochondrial transfer in oocytes (Rudat, 2013). This might indicate that the general public favors national regulation over case-by-case involvement of regulators rather than indicating a cultural difference between the Netherlands and the UK or a difference between reproductive techniques. Our findings are in line with almost all (97%) respondents of a UK survey supporting regulating germline genetic modification (Wiperman and Campos, 2016).

The fact that a bioethics committee was preferred as the regulatory body rather than a medical professional association, is in line with the view that medical doctors are not experts on the societal consequences of fertility treatments alongside the fear of their potential over-eagerness to treat in order to gain money or status (Daniels and Taylor, 1993; Furger and Fukuyama, 2007; Harper et al., 2012). In addition, a bioethics committee may be better equipped than a medical professional association or a government to address the negative consequences that they will regulate as this requires weighing conflicting values such as protecting patients from maleficence versus supporting patient's reproductive autonomy. The regulatory body will, for example, define on a national level which exact risk on major congenital abnormalities is acceptable whilst leaving the decision to accept a risk under this limit up to patients. As previously shown among the general public for priority setting in health care and for regulating germline genome modification, the three questioned stakeholder groups want the regulatory body to consult with advisors from different backgrounds (Wiseman et al., 2003; Trust, 2005; Wiperman and Campos, 2016). The fact that, besides a national bioethics committee, gynaecologists were the most popular advisors, according to the three participant groups, is in line with a medical professional association being named as advisor for other health care decisions, such as the allocation of health care resources (Dolan et al., 1999; Wiseman et al., 2003). Our findings support the previous request (Blank, 1990; Singer et al., 2000; Dolan et al., 2003; NICE, 2005) for regulatory bodies to take account of all potential negative and positive health and societal consequences of a novel technique not only those that they are mandated to regulate. More specifically, all potential negative and positive consequences of stem cell-based fertility treatments were valued by at least one in 10 participants. Some negative consequences that did not receive majority support for regulation in a certain group of respondents were even important to the majority of that group (e.g. only 28% of patients supported regulating success rates, while success rates were important to 80% of them).

We questioned the need to regulate the clinical implementation (i.e. use in day-to-day clinical practice) of a novel reproductive technique. This differs from evaluating novel techniques in the context of clinical

research, which requires approval from a national or institutional (ethical/review) committee in virtually all countries (WMA, 1964). The clinical implementation of novel techniques has long been less strictly regulated than the clinical implementation of novel medications or medical devices (Spodick, 1975; Margo, 2001; Lindvall and Hyun, 2009; Dondorp and de Wert, 2011; Strasberg and Ludbrook, 2003). The clinical implementation of novel medications, for example, has to be approved by a special regulatory agency (e.g. American Food and Drug Administration or the European Medicines Agency), which requires reassuring results from preceding clinical trials. The regulation concerning the safety of the clinical implementation of novel cell therapies, such as stem cell-based fertility treatments, is more recent and is being developed further (e.g. regulation 1394/2007 of the European Parliament). Our study shows that stakeholders from three different groups would encourage policy makers to set up a national bioethics committee regulating the clinical implementation of stem cell-based fertility treatments. Our stakeholders align with the European regulation that this committee should mainly focus on major safety concerns but additionally encourages the committee to take account of all other potential consequences of techniques and to consult with advisors from different backgrounds during this process.

If the regulatory body allows the clinical implementation of stem cell-based fertility treatments based on an expected risk of adverse outcomes, it should assure that the actual risk of adverse outcomes is monitored afterwards (Mandel, 2009). The regulatory body could, for example, require clinics using the technique to keep a registry with specific outcomes and a specific structure to later on pool the data from different clinics (Land and Evers, 2003; Mandel, 2009). Additionally, once the actual risks are revealed by the registry, the regulatory body should meet and reconsider whether the technology should still be used in clinical practice (Mandel, 2009).

Furthermore, allowing a technique under certain conditions, implies that the regulatory body organizes a system to license and inspect clinics performing the technique. If the regulatory body would be a national bioethics committee, consulting with medical specialists (i.e. the regulatory body and advisors receiving majority support from our three stakeholder group), they could outsource providing licenses and performing inspections to existing and experienced governmental agencies (Mandel, 2009).

Further research should examine whether the documented broad support from Dutch stakeholders for regulating stem cell-based fertility treatments can be generalized with regard to other countries and to other (reproductive) techniques such as germline genome modification. The support for regulating reproductive techniques might be lower in countries with cultural objections against donor conception, with a strong pro-natalist ethos, or with minimal legal restrictions and this is relevant as (fertility) patients may seek cross-border care. The need to prevent fast implementation of potentially ineffective or harmful novel techniques might be considered less apparent for treating patients with life-threatening diseases (e.g. cancer) than for treating infertile patients, where the techniques might also affect their offspring (Schatten, 2002). Nevertheless, professionals from fields relying on other than reproductive (e.g. surgical) techniques, have also called for regulating the introduction of novel techniques (Spodick, 1975; Grimes, 1993; Margo, 2001; Lindvall and Hyun, 2009; Strasberg and Ludbrook, 2003). Rather than developing a tailored regulatory framework for each new technique, it would seem logical to develop

categories of techniques based on their potential clinical and societal consequences that can be judged accordingly (Mandel, 2009). For instance, it would make no sense to judge a novel suturing technique in the same way as germline genome editing. Categorizing new techniques is surely challenging but has been previously reported feasible for surgical techniques (Reitsma and Moreno, 2005). Following this line of thinking and in line with our current findings, new techniques in reproductive medicine are likely to be judged rigorously given their potential health effects for future offspring and their societal sensitivity. Our findings among three important stakeholder groups may encourage policy makers and professionals from different fields to reflect on the need to regulate the clinical implementation of novel techniques.

## Supplementary data

Supplementary data are available at *Human Reproduction* online.

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## Authors' roles

S.H. contributed to the study design, data collection, analysis, manuscript drafting and critical discussion. E.A.F.D. contributed to the study design, manuscript drafting and critical discussion. S.R. and R.V. contributed to the study design and critical discussion.

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None declared.

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