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Evolving minimum standards in responsible international sperm donor offspring quota

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Short title: International sperm donor-offspring quota

Evolving minimum standards in responsible international sperm donor offspring quota

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Abstract

An international working group was established with the aim of making recommendations on the number of offspring for a sperm donor that should be allowable in cases of international use of his sperm. Considerations from genetic, psychosocial, operational and ethical points of view were debated. For these considerations, it was assumed that current developments in genetic testing and Internet possibilities mean that, now, all donors are potentially identifiable by their offspring, so no distinction was made between anonymous and non-anonymous donation. Genetic considerations did not lead to restrictive limits (indicating that up to 200 offspring or more per donor may be acceptable except in isolated social-minority situations). Psychosocial considerations on the other hand led to proposals of rather restrictive limits (10 families per donor or less). Operational and ethical considerations did not lead to more or less concrete limits per donor, but seemed to lie in-between those resulting from the aforementioned ways of viewing the issue. In the end, no unifying agreed figure could be reached; however the consensus was that the number should never exceed 100 families. The conclusions of the group are summarized in three recommendations.

KEYWORDS:

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<A>Introduction

Medical, social and economic developments, and a sense for opportunities among entrepreneurs, have given rise to the development of gamete banks providing reproductive services and material to patients around the world. These international services are accomplished either by people travelling for treatment to clinic(s) local to the donors, or by clinics exporting the reproductive material abroad. Services are readily arranged through present-day facilities such as the Internet, through reliable material transport facilities and as a result of the easy and increasingly affordable nature of international travel in modern society.

Most countries regulate the assisted reproduction technique activities within their borders (Gong *et al.*, 2009, Janssens *et al.*, 2011). Cross-border activities, however, with some rare exceptions (Spanish guidelines, German guidelines; Código ético de la SEF, 2012; Thorn and Wischmann, 2013) defy national recommendations, regulation and supervision. There are international recommendations, suggested in papers (Blyth *et al.*, 2011; Thorn *et al.*, 2012) and in a guideline from ESHRE on cross-border reproductive care (CBRC) (Shenfield *et al.*, 2011). These recommendations, however, are generally stated and not legally binding. In addition, no international body with relevant regulatory powers exists to oversee assisted reproduction technique activities.

One of the issues provoking regular debate concerns the number of offspring a gamete donor reasonably may have. We denote this issue here as ‘donor quota’. The European Union Directives on Cells and Tissues (2004/23/EC, 2006/17/EC, 2006/86/EC) were enacted with the aim of protecting the health of donors and recipients and to increase the availability of safe cells and tissues. Meeting these laboratory standards constitutes a legal basis for the exchange of donor sperm between approved tissue facilities within the European Union and, of course, increases the availability of donor sperm throughout the European Union. How to combine this with differing national guidelines and legislations, however, including those on donor quota, is more complicated.

Basic to the issue of donor quota is the fact that a man is able to produce an effectively unlimited number of ejaculates to sire potential offspring without physical risk to himself. International use of donor sperm is a common practice, as shown by various sperm banks operating internationally. The international distribution of sperm, however, is unregulated. This international use of donor sperm, either distributed from sperm banks to multiple countries, or provided to foreign recipients travelling to local clinics, opens the possibility for these donors to have more offspring than donors whose sperm is used only on a regional or national scale. In an effort to establish recommendations on the number of offspring, a donor whose gametes are used on an international scale may have, a working group of professionals from different European countries and professional backgrounds was established in 2012. Discussion within the working group rapidly led to the conclusion that any arguments on donor quota should take into account considerations from the field of genetics, psychology and social science, ethics, operational and legal aspects. Following a section considering the general considerations relevant for the issue at stake, we here describe the views put forward on each of these topics in the debates held within the working group.

<A>General considerations

As a starting point for our discussions, it was noted that the existing national quota in different countries ranges from one (Taiwan) to no limits (Canada, Sweden) (Janssens *et al.*, 2011). In some countries, professionals formulated the standards whereas, in others, politicians and Governments responding to ‘public’ concerns proclaimed the directives and laws. The wide range of quotas suggests that different arguments have been used in different countries, but also reflects variation in cultures, including the weight given to science, religion, professional insights, beliefs about kinship structures and public opinion on management of matters in reproductive medicine (Gong *et al.*, 2009; Janssens *et al.*, 2011; van Hoof and Pennings, 2012). The international use of donor sperm may differ in some characteristics from the national use of gametes (**Table 1**), although some arguments playing a role in national donor quota are likely to be relevant for international donor quota as well.

A point of unanimity among the panel was that best practice in regulation should limit donations by numbers of ‘families’ rather than children or pregnancies. This allows families to be completed using one donor alone (if this is desired by parents), a principle that is broadly considered an optimal way of family building through donor insemination. Counting in terms of individual children (or pregnancies) risks the possibility that, at some moment, the permitted limit is reached before mothers having a child from a certain donor apply for another insemination, which then would have to be refused (or lead to use of another donor). Leaving aside any discussion on whether families function better or not when children are genetic siblings, such a system also reduces any risks attached to later contacts where more than one donor is involved in one family, such as one donor providing fuller information about themselves or being more receptive to contact than another.

Obviously international donor quota cannot be applied independently from national quota. If national regulations restrict the distribution or the use of gametes from or to another country, then institutions and professionals have to adhere to those national limits. In the international sphere, regulations from both the distributing and receiving country must be taken into account. As a result, the possibilities for using gametes on an international scale will vary. When considered in more detail, distinction should be made between regulations on distribution and acceptance of gametes to or from abroad (**Figure 1**). Some countries have none of these, some have one or the other and some have both. The country with the strictest limits and regulations will usually determine the final result. In two-thirds of the situations, national quota are decisive because either rules on distribution or rules on acceptance have to be dealt with (**Figure 1**, orange fields). In the case of distribution to multiple countries, the distributing country may distribute to a certain limit determined by all separate national quota combined until the quatum of the distributing country is reached (or any other internationally recommended quatum). In the case of receiving patients from multiple countries determining limits will be those of the receiving country, meaning that the total number of offspring conceived internationally could exceed those of the patient’s country of origin. Obligations normally (if not always) apply to professionals and official institutes (clinics, hospitals) which are supervised by the relevant local authorities and often obliged to have a license to perform their work. Rules related to institutes may sometimes also apply to private individuals, although individuals are more complicated to regulate. For example, in Spain, institutes are not allowed to deliver gametes to private individuals, which does not preclude them making

arrangements directly with each other over the internet. The latter in turn has its own health risks and concerns.

<A>Genetic considerations

Genetics was considered important by the working group owing to both the potential effect of the number of offspring on the likelihood of possible consanguineous relationships (inbreeding), and on the propagation of genetic diseases. These topics are treated independently in the following sections and fear of consanguinity is dealt with in the following section.

Consanguinity

Calculations have shown that, in a system with anonymous donors, up to 25 offspring per donor for a population of 800,000 does not lead to an increased chance of consanguinity by accidental contacts between donor-offspring being half siblings unwittingly (de Boer *et al.*, 1995; Sawyer *et al.*, 2008). New calculations were made for systems with non-anonymous sperm donation and a significant proportion of single and lesbian women requesting sperm donation (working group in collaboration with Dr Repping and Dr Zwinderman; calculations online and available at request). From these calculations, it followed that for a population of 16 million, if up to 200 offspring-per-donor were permitted, the number of unexpected consanguineous relationships among donor children was 0.2%. The number of consanguineous relationships being initiated between donor children not knowing the identity of their genitor (donor 'father') for a population of 16 million (200,000 annual births) was calculated to be 0.418 per year (**Table 2**). The essence is that offspring who know they are conceived via donor insemination, and know exactly who their donor is, will not mate with one another. It was assumed that this is the case for offspring born from single women, lesbian relationships and heterosexual relationships in which the parents inform their offspring about the use of donor insemination. For the calculations, the proportion of these family types were assumed to be one-third each, whereas the number of heterosexual couples telling their offspring about the donor insemination was taken to be 50% (Janssens *et al.*,

2011), resulting in 16% of all donor insemination offspring remaining unaware of their specific conception and being at risk of inadvertent consanguineous mating. Indeed, the contribution of donor-offspring-mating to the occurrence of inbreeding in society as calculated is deemed insignificant compared with other kinds of mating in modern society, as shown in a recent study by Serre *et al.* (2014). These authors showed that donor insemination would account for only 0.46% of the consanguineous births and for 0.01% of the recessive diseases occurring in France. This suggests that most inbreeding-based national norms quota applied in donor insemination are within safe limits, if not at a too stringent level. For use of donor sperm internationally, implying distribution over larger populations rather than within single countries or districts, the chances of inbreeding are even smaller.

When donors are used to treat patients in small defined geographical areas, however, particularly if this involves minority groups, the relevance of consanguinity and these figures should be taken into account.

The 2013 American Society for Reproductive Medicine recommendations suggest that ‘in a population of 800,000, limiting a single donor to no more than 25 births would avoid any significant increased risk of inadvertent consanguineous conception’ (ASRM, 2013). This 1:32,000 birth limit would theoretically permit a donor to give rise to around 250,000 children worldwide at the current world population, although other considerations would in reality lower this. It is, therefore, clear that worries around consanguinity will not provide the decisive arguments to come to acceptable donor quota.

Propagation of genetic diseases

In recent years, regular suggestions have been made to screen for specific prevalent genetic diseases or just to control the spreading of genetic diseases by decreasing the number of offspring per donor (Watson *et al.*, 2004; AATB *et al.*, 2008; Prior, 2008; Maron *et al.*, 2009; Callum *et al.*, 2010, 2012; Hansen, 2012; JydskeVestkysten, 2012). Some centres already systematically screen all donors for certain mutations (Sims *et al.*, 2010). Mutations and genetic diseases, however, are present in all populations. In a recent study testing mutations

for 108 recessive genetic disorders on 23,500 individuals, 24% of them were found to be a carrier for at least one recessive genetic disorder (Lazarin *et al.*, 2013), whereas in a study testing mutations for 448 disorders in 104 random DNA samples, individuals were found to carry on average three recessive disease mutations (Bell *et al.*, 2011). This means that propagation of genetic disorders can never be fully prevented.

As new genetic technologies testing for many thousands of mutations become available, this may in effect reduce any unknowns far below current standard risk-practice levels (Dondorp *et al.*, 2014). The clinical utility of these techniques, however, is yet to be determined and undirected risk profiling is considered disproportional by many authors (Dondorp *et al.*, 2014; Winand *et al.*, 2014). This raises the question as to whether a level of safety should be required for donor insemination that is not reached in the wider society.

Irrespective of the answer to this, the spreading of genetic diseases taken together is not affected by the number of offspring a donor may have. We are aware of the fact that this is counterintuitive at first impression, but this is the conclusion that logical scientific reasoning leads to. Obviously, the number of offspring carrying a certain genetic disease will be higher when a donor carrying that specific disease has more offspring. As donors are a random selection from the general population, however, the chance that a donor carries an unidentified genetic disease is balanced by the chance that he is not a carrier of such disease: donors not carrying genetic diseases have more offspring to the same extent as those carrying the disease. In other words, the increased propagation of certain genetic diseases by donors having many offspring is compensated by the increased propagation by donors not carrying genetic disease. This holds for any genetic disease, be it recessive genetic diseases like cystic fibrosis, spinal muscular dystrophy and hypertrophic cardiomyopathy (Prior, 2008; Maron *et al.*, 2009; Callum *et al.*, 2010; Sims *et al.*, 2010), or late onset to low penetrant autosomal dominant genetic diseases not apparent at the time the donor was active (e.g. autosomal dominant cerebellar ataxia and neurofibromatosis (Janssens, 2003; Callum *et al.*, 2012; Hansen, 2012). Having many offspring will result equally well in greater distribution of 'good' genes as it does in the propagation of 'defective' genes. Therefore, compared with the general population, an individual using donor insemination does not have an increased risk of obtaining children carrying or manifesting genetic disease as a result of higher offspring

numbers per donor, as described previously (Janssens, 2003). Note that donors are, in reality, even more 'genetically' healthy than a random population selection, because they are screened by a health check, taking their family history and on top of that sometimes genuine genetic testing. Similarly, as for individual donor conceived children, at population level the propagation of genetic diseases, all types taken together, is not increased by donors having more offspring. The offspring number affects only the impact the discovery of the propagation of a certain inherited disease has, and of course the propagation of that very one disease, plus the chance that some genetic defect originating from any donor will be encountered among offspring. This chance increases with increasing numbers of offspring per donor, simply because of the fact that the chance for obtaining homozygosity of recessive genetic disease of any type increases with the number of offspring. Also, the chance of manifestation of low penetrant diseases, undiagnosed at the time the donor is active, is increased. There is no rationale, however, in decreasing the number of offspring per donor because of the fact that genetic diseases are more often manifested with increasing numbers of offspring per donor, as the offspring number has neither an effect on the chance of having genetic disease among donor children or them being carrier of such a disease, nor on the prevalence of genetic diseases in the population.

Another point of discussion is that newly evolving genetic techniques not only enable donors to be cheaply screened and matched against recipient patients, they will also result in the discovery of increasing numbers of misattributed paternity cases and close or more distant relationships of which individuals were previously unaware (Borry *et al.*, 2014). Parents should be made aware of such potentially unanticipated outcomes during discussions before the use of treatment using donor gametes as should potential donors in discussions about the limits of privacy protection. In fact, these implications of genetic testing refer to the psychosocial impact and implications of genetic testing. The opinion of the working group was in agreement with the conclusions of others (Scheib and Ruby, 2009, Sawyer, 2010, Sydsjö *et al.*, 2014) that risks for consanguinity and propagation of genetic diseases or traits are in themselves not a compelling reason for low donor quota, except in instances where small or selective (ethnic) populations are involved. Considerations other than those related to genetics seem to be more important in determining the acceptable offspring number per donor.

<A>Psychosocial considerations

Psychosocial considerations in the case of donor insemination are essential to evaluate the interests of the different stakeholders: donors, parents and offspring. From a theoretical perspective, donors may envy, be neutral, or be overwhelmed by having many offspring, and possible contact with donor offspring. Parents, at best (most probably), will be neutral, but more likely may well feel offended by donors seeking contact with them or their donor offspring, although exceptions with positive experiences exist, especially in single mother and lesbian relationships. Offspring may be neutral, be curious or be longing to know their donor and to contact them. It is important to remember that, in addition to the primary mentioned stakeholders, any relatives of stakeholders may also be affected by donor-related experiences. Such considerations include the experiences, opinions, feelings and expectations of each party the interactions that the stakeholders may have with each other, and the social context within which this takes place.

Prima facie it seems useful to make a distinction between systems with guaranteed anonymous donors and donors whose identity may be released to the offspring (for an overview see Janssens *et al.*, 2011). In anonymous systems, the expectation is that donors, offspring and 'donor siblings, will normally never have contact, suggesting that the contact argument counts differently in each system. It is doubtful, however, whether it is wise to preserve the distinction between anonymous and open-identity systems in view of the modern developments in information and communication systems (the Internet) and in DNA-technology and matching techniques (Sawyer, 2010). In the long run, parents in anonymous systems may not be able to keep secret their chosen method of conception, and donors may find their privacy breached by donor offspring using increasingly sophisticated methods to trace them. When one also takes into account the mobility of people that result from improved access to travel, it seems reasonable not to take into account regional or even national quota. An anonymous donor will usually experience fewer consequences of his donation, because the offspring (and parents) do not know him, so cannot easily seek contact, as long as the anonymity is preserved. In view of that, the only psychological arguments to be considered

for anonymous donors would relate to the idea the donor has in his mind when doing his donation (i.e. what he considers acceptable and reasonable as offspring number — offspring that would never know him). Seen from this perspective, any quota on offspring might be permitted to be less stringent for anonymous donors than for non-anonymous donors. The latter would be likely to experience much more from their donation, so may be expected to request more stringent quota. By treating the issue only from the perspective of non-anonymous donation, we suppose we will end up with the more stringent figures, which only will overtly be more safe for anonymous donors if they were traced, as described in our genetics discussions above. Moreover, half-siblings from either anonymous or non-anonymous donations are nowadays already as likely to trace each other if they wish, using molecular genetic methodologies. This led us to make no distinction between anonymous and open identity systems in our psychosocial considerations.

Striving to make recommendations on donor quota, argumentation based on psychosocial evidence brings a challenge, as the different stakeholders in donor insemination can have widely differing opinions, feelings and expectations. Even within groups of stakeholders, the opinions, feelings and expectations can differ widely (Kirkman, 2003). In addition, there is as yet only a limited body of psychosocial research available, using a limited range of methodologies and drawing on small numbers with a potential for bias that will not be understood more fully until greater numbers are conducted (for a review see Blyth *et al.*, 2012). Much existing research is qualitative research and hence does not seek to evaluate the different perspectives of the stakeholders but instead to increase understanding of the range of views (Mason, 2002). No studies were found with a sole focus of gauging views on donor quota.

With that in mind, a growing body of psychosocial research indicates the potential complexity of managing new relationships and contacts following the ‘matching’ of genetically related parties, be that between donors and offspring, ‘donor siblings’, or parents whose children were conceived using the same donors (Freeman *et al.*, 2009, Scheib and Ruby, 2009; Jadva *et al.*, 2010; 2011; Hertz and Mattes., 2011; Blyth 2012a; Hertz *et al.*, 2013; Kramer and Cahn, 2013; Kirkman *et al.*, 2014).

In a study concerning 63 German donors, 19% considered the national limit of 15 offspring per donor appropriate, 11% considered it too high and 27% too low (43% had no opinion), (Thorn *et al.*, 2008). A recent survey among 21 sperm donors registered with a UK-based DNA-based voluntary contact registry showed that most sperm donors (13) imposed no limit on the maximum number of offspring conceived with their gametes and one would accept 'more than 20', whereas four would feel comfortable with five to 10 offspring and one fewer than five (van den Akker *et al.*, 2015). These figures suggest that many donors consider rather high limits acceptable, but taken into account should be the fact that these data are from men that are interested in the outcome of their donation, which may lead to higher limits. Also, in a study among Danish sperm donors, 71% of the respondents said the offspring number did not matter; it might even be higher than 100 (Bay *et al.*, 2014). A survey among 47 donors in the Netherlands reports that donors on average choose for 20 offspring per donor, whereas almost one-half accepted the 25 offspring allowed according to the professional Dutch directive (Winter *et al.*, 2012). Rather contrasting with these figures are the results of a recent paper reporting on the attitude of Swedish gamete donors, showing that one-half of the sperm donors think that the offspring from a single donor should not exceed the number of 10, whereas 13% thought it should be limited to 15 (Sydsjö *et al.*, 2014). Only some 12% of the donors in this study considered more than 30 or an unlimited number of offspring per donor acceptable. One study actually reported a donor having concerns about managing large numbers of offspring (vaguely specified as something like 14–27), should they appear (Crawshaw *et al.*, 2007). An internal survey of UK DonorLink Registrants Panel's views about donor limits in 2012 (surveying offspring and donors), (Crawshaw, personal communication) and a German survey on parental attitudes (Thorn, personal communication) indicated that, according to a small majority of the respondents, the number should not exceed 10 offspring or families per donor. Donor offspring in the UK DonorLink survey were inclined to favour lower limits than were donors and in addition more likely to believe that any limits should include the donors' own children. The former was not found in the survey of van den Akker *et al.* (2015), in which 62% of the donor offspring said to find 'no limits' on the number of siblings acceptable (63 responding donor offspring), so a majority, and a figure comparable to that of the donors. A survey among UK parents, patients, donors, offspring and the general public found that, although the number of families helped by one donor should go no higher than the UK limit of 10 (the UK guidelines count in

families not offspring), a number which could potentially lead to about 20 offspring per donor (<http://www.hfea.gov.uk/5605.html>). Where surveys were conducted in countries with national donor quota in place such as the Germany, UK, Denmark and the Netherlands, it should be noted that this may have influenced responses, with figures tending towards the status quo, as a hard-to-prevent effect of the well-known psychological anchoring and framing effects (Kahneman, 2011).

A survey on donor insemination recipients registered at the American Donor Sibling Registry (DSR) showed that 75% of 621 respondents preferred offspring limits between 1 and 10, with 43.2% indicating exactly 10 offspring per donor, whereas a small proportion (5.0%) of respondents thought that as many as 25 is acceptable. In addition, 78% of 1562 respondents indicated that donors should be restricted in donating at more than one semen bank, heterosexual-couples and single women being more in favour of this than respondents from lesbian relationships (Sawyer *et al.*, 2013).

Systematic studies on the opinion of *offspring* on donor quota could not be found, although in some articles it has been reported that offspring (Kirkman, 2003, 2004; Cushing, 2010; Rodino *et al.*, 2010; Allan, 2012; Blyth 2012a; 2012b), and on occasion donors (Crawshaw *et al.*, 2007) mention general concerns about accidental consanguineous relationships. Many professionals in the field, however, find the extent to which such expressions of concern from self-selecting respondents (who may be those with the strongest desires and convictions) should influence the debate is difficult to determine. As with any developing field of research the use of data to assist discussion of setting donor quota is limited by the dearth of controlled studies with which to augment the growing understandings offered by qualitative studies with limited selection criteria.

Given the limited research evidence base and that the focus of much psychosocial research is on the complexity and ambiguity of human reactions, interpretations benefit from also drawing on the practice experiences of psychosocial professionals and the theoretical frameworks that are widely used to understand child development and family systems (Featherstone, 2009). Of potential significance is the family size norm in a given culture at a

certain moment and the number of offspring with whom a donor may seem likely to manage an ongoing relationship or the number of ‘donor siblings’ relationships that appear manageable, if desired. In situations in which donor-siblings have met, no differences have been reported in the experiences among donor offspring in terms of whether they were in small or big groups (Jadva *et al.*, 2010); elsewhere, however, higher numbers have produced challenges that need to be managed as well as rewards (Hertz and Mattes, 2011; Blyth *et al.*, 2012). The nature of any relationships resulting from ‘matching’, whether they are intimate and long-lasting, and whether they will form a burden or be a pleasure for those involved is currently little understood. The likelihood is that there will be a range of experiences, related in part by the motivation behind searching. It should also be borne in mind that the effect and implications can spread to each party’s existing kinship and social networks too (Beeson *et al.*, 2013).

Overall, this might be taken to suggest that high offspring numbers might well, but should not necessarily, be deleterious. To be on the safe side, however, the psychosocial point of view led to the conclusion that no more than 10 families per donor is reasonable, noting our recommendation that the numbers be discussed with donors, prospective parents, children, regulators and the public, in the context of ‘families’. It is of course worth recognizing here that, in any system, the donors themselves should have a say and determine a lower maximum number of families to be created from his gametes than allowed according to the accepted donor quatum. We think that this is reasonable and in line with Western culture, because a donor gives something with great potential consequences, possibly also for himself (in cases where he would be identified). Also, as semen banks are (naturally) in need of having donors, it is not unwise to accommodate to reasonable wishes of donors.

<A>Operational considerations

Operational and legal aspects are important because they concern the feasibility and implications of recommendations and measures to be taken. Strict rules and low donor quota can result in waiting lists, hampering treatment of recipients (Blyth and Frith, 2008). The cost of recruitment of donors is high (Tomlinson *et al.*, 2010), which has to be balanced by the revenues. Inefficient or insufficient use of donated material makes the business uneconomic

and sooner or later leads to closure of facilities (or impossibility to start new ones), resulting in failure to create families and longer waiting lists elsewhere. Of course this is unfavourable to those seeking help with reproduction as it may lead to a poorer service to them, and uncomfortable side-effects for the professionals who are employed in the business. Patients (and potentially donors), who are not satisfied at home may go abroad, as has occurred in Scandinavia, Italy, France and other countries (Ernst *et al.*, 2007; Pennings *et al.*, 2008; Farraretti *et al.*, 2010; Shenfield *et al.*, 2011; Rozée Gomez and Rochebrochard, 2013). In some countries, this careful weighing of interests, including that of business, has taken place, for instance in Denmark, the country housing some of the world's largest sperm banks (Herrmann, 2013). It depends on society, politicians and professionals to act responsibly and facilitate a service that works, minimally for its own citizens, or change things for the better.

The preceding considerations might lead to the conclusion that, from the business point of view, there should be no restrictions to the number of offspring per donor. It might seem the more, the better, as waiting lists will be shorter, clients more satisfied, the use of gametes more efficient, and the profits higher. This is a too simplistic a view, however. Business-driven professionals may also feel compelled by genetic, psychosocial and ethical considerations as described. But no less significant is it for the business to prevent that it is hit by bad news. Such a situation may occur in the case of malfunctioning, irresponsible care, errors or incidents and provocative reporting. High numbers of offspring from donors (New York Times, 2011; National Post, 2011; The Telegraph 2012; Nationalt, 2013; HuffPost Style, 2014) or seemingly irresponsible donor quota may lead to public doubts and criticism, as crucially may also the finding of offspring with diseases traceable to donors and the semen bank (i.e. congenital, genetic or epigenetic; Sheldon, 2002; Maron *et al.*, 2009; Callum *et al.*, 2012, Hansen, 2012; JydskeVestkysten, 2012). The latter relates to the fact that the chance of encountering donor offspring with genetic diseases increases with increasing numbers of offspring per donor, as was explained before (see section on genetics). Negative publicity is bad for the business and service in general, even when the activities were carried out responsibly, according to accepted procedures. Commercially driven clinics will do the utmost to advertise a picture of credibility, quality and competitiveness with regard to success rates towards potential users (Sarojini *et al.*, 2011).

A practical point relates to the supervision and control in international distribution of sperm. The donor offspring that are born have to be recorded. Presently, this is done at a local level or national level. As yet, it is not clear what is preferable. The unique recording of internationally used gametes will be helped by application of the unique coding system, to be introduced for donors in Europe (Reynolds *et al.*, 2010). Care should be taken to prevent incomplete feedback about pregnancies as occurred in other records of pregnancies (Mikolajczyk *et al.*, 2013). This seems all the more difficult in cases of international use of sperm and pregnancies achieved in multiple countries. Reporting by institutions is likely to be more complete and consistent than from private individuals. This may require special attention for the latter. Obviously, European regulation will not be sufficient for supervision of cross-border reproductive care in which countries outside Europe participate. Having European regulation, however, may be a good start for arranging more responsible cross border reproductive care and gamete use according adopted donor quota.

<A>Ethical considerations

The ethical question is whether it is morally right to have a policy that puts some form of limits on the number of offspring produced from a donor. On what grounds could donors, recipients, sperm banks and professionals be asked to alter or constrain their practice? This can be seen as a form of liberty-limiting question. As liberty is usually presumed to be a good, we need good ethical reasons for stopping someone doing something. The main grounds for this are that allowing someone to exercise their liberty results in harming someone else (Feinberg, 1973). In other words, the burden of proof should reside with those wishing to restrict choices. Dahl (2007) sums up this argument when he says, ‘each citizen ought to have the right to live his life as he [*sic*] chooses so long as he [*sic*] does not infringe upon the rights of others. The state may interfere with the free choices of its citizens only to prevent serious harm to others’ (p. 158).

The central claim is that personal reproductive decisions and choices should be free from interference, unless they will cause harm to others. Any extension of choice is frequently portrayed as desirable, and this is just as true for reproductive choices. Reproductive choice

has been one of the main arguments used in favour of restricting regulation of assisted conception. Advocates of reproductive autonomy (e.g. Savulescu, 1999; Harris, 2004) endorse the pre-eminence of reproductive choice in most circumstances. This argument is sometimes reinforced by claims that reproductive choices are 'integral to a person's sense of being' (Jackson, 2007, p. 48). Any restrictions, therefore, require even more robust justification than less important choices (Robertson, 1994). So, as reproductive choices are very important allowing people to exercise them is a good in itself and this good outweighs the production of a certain level of harm. In sum, there is a belief that the more important the particular choice, the stronger the case for restricting it has to be. In the area of donor quota we can ask: does imposing some level of quota lead to harm, or does the absence of quota lead to harm? As has become clear from the previous sections it is not evident how much harm or benefit accrues to particular donor quota.

It could be argued that donor-quota restrict the reproductive autonomy of those seeking treatment. A low donor quota would limit the availability of donor semen and therefore semen banks would have to recruit more donors. Also the price of treatment may increase. Taken together, this will potentially prevent many from receiving treatment. High donor quota on the other hand might be unpopular with certain parents (i.e. because of fears about accidental consanguineous relationships that offspring may have). The fears of people may well not be entirely rational, with people being inclined to overestimate the chances of unlikely or improbable risks, as psychological research has shown (Kahneman, 2011; Peters *et al.*, 2011). Still, the fears by themselves are real and have to be taken into account. Converse arguments also exist. Recipients might like the idea of low donor quota as that will mean there is a lower likelihood of their child having many siblings or half-siblings being raised in other families. Donors (in open identity systems) may also welcome limitations on the number of possible offspring, as they may fear that too many offspring might seek contact. Anonymous donors may be less affected by these considerations, unless they are made aware of, or otherwise fear, the possibility that they may anyway be traced.

Taking into account the ethical interests of donor offspring, donors and recipients is crucial as they are the major parties in donor insemination. Offspring arguably have a distinct status as they cannot agree or disagree with being conceived and in this context they are not able to

exercise any form of choice. The professionals being involved in donor insemination might be expected to have the role of guarding the interests of the offspring, but what would this exactly lead to? What level of donor quota is less harmful for donor offspring is unclear. At best, it has been observed that some donor offspring apparently relished having half-siblings, knowing that they are a part of extended families (Freeman *et al.*, 2009). The section on psychosocial considerations has shown, however, that the emerging picture is more complex and wide ranging from one individual to another. Therefore, having a large number of half-donor-siblings may be perceived as a harm by some and a benefit to others. Further, there is, as noted above, a growing body of research charting the challenges of managing these complex 'kinship relationships'.

Although it might be unclear what harm differing donor quota may produce, a further question is how we balance harm across groups — whose interests to prioritize? Although reproductive autonomy might be a laudable principle to use in this area, how do we determine whose autonomy we prioritize and what happens if peoples' interests in exercising their choices conflict? In the UK, the principle of the welfare of the child has been seen as one of the guiding principles of regulation, as demonstrated by arguments used to justify removing donor anonymity in 2005 (Frith, 2014). It could be argued that as donor offspring are the only party who are unable to consent, and they start off initially as vulnerable children, it is their interests that should take priority. As mentioned above, however, it is not clear how, in reference to donor quota, their best interests are served.

One element of donor offspring's best interests is what view is taken on the significance of the relationship between donor offspring and their donor and how different levels of donor quota might impact on this. A number of donor offspring think that this relationship is important and will help them feel more complete in their own identity. This, one way or another, also appears to be a strong belief among the general public. It seems most donor offspring are only curious about their donor and are not seeking a (another) father, however (i.e. being interested in what the donor looks like, how he talks, what his convictions are, what kind of character he is and family medical history). As the significance of this relationship, information, or both, varies between individuals, determining the number of offspring per donor requires attention to the psychosocial aspects of donors, donor offspring

and parents. It is notable that various studies report that many donors often think about their donation and resulting offspring (Van den Broeck *et al.*, 2013; Kirkman *et al.*, 2014). Some of them fear possible contact, whereas others yearn for having contact with their offspring. Of course, those believing in actual consequences of the genetic ‘bond’, in other words, those with a ‘mind-set’ that donor offspring and donors have a kind of parent-child relationship, will quite certainly also agree with the weight given to psychological arguments in determining the donor quota. Those, on the other hand, who consider the idea of a parent-child relationship between donors and offspring aberrant, are inclined to trivialize the importance of psychological arguments in determining donor quota. They argue that genes can be shared with many people, but feelings or relatedness do not automatically follow from genetic relatedness.

The ethical aspects of donor quota depend on the level of harm perceived to be caused by either restrictive quota or unlimited quota. In terms of the genetic argument there seems to be little harm; psychosocial aspects depend to a degree on how the donation is perceived (as part of family formation or as a medical procedure of donating tissue); and operational perspectives suggest concern for safety and public confidence in their activities, that arguably could be furthered by reasonable donor quota. It seems prudent, in the absence of clear evidence, to adopt policies that recognize the potential for harm created by large donor quota and have some reasonable limits in this area.

<A>Discussion

Developments in donor insemination over the last decade have resulted in a wish for recommendations on the number of offspring that a single sperm donor reasonably may have when his sperm is used on national scale or distributed internationally (Janssens, 2003; New York Times, 2011; National Post, 2011; Callum *et al.*, 2012, Hansen, 2012; Daily Mirror, 2012; The Guardian, 2012; The telegraph 2012; Nationalt, 2013; HuffPost Style, 2014). In cases in which very large numbers of offspring from a single donor have been reported in the news, parents, donors, medical experts and indiscriminate commentators and journalists have expressed concerns about the consequences for donors or offspring. These are frequently

accompanied by appeals for regulation of the activities in reproductive medicine, including setting more responsible offspring numbers per donor (New York Times, 2011; National Post, 2011; JydskeVestkysten, 2012; HuffPost Style, 2014). Acting responsibly and transparently is no doubt also a wish of professionals, irrespective of medical incidents or exceptional donor cases. Given the multidisciplinary professional interests involved in donor insemination an international working group with members of diverse professionals (laboratory specialists, physicians, psychosocial professionals, scientists, ethicists and business-men of different nationalities, active in commercial, university and community hospital-based institutions) was formed to explore the issue in depth.

Perhaps not surprisingly the arguments resulting from different professional insights, personal standpoints and interests do not lead to straightforward recommendations. This situation is presented in **Figure 2**. It should be noted that the ordinate of this figure has no numbers as it does not represent concretely available data. The lines are meant to indicate trends, to clarify the divergent arguments. When the number of offspring per donor is set low, there are likely to be problems of accessibility to donor gametes for users, while the operation of the sperm bank will become uneconomical. Causing insufficient supply may also be considered unethical, alien to social justice. Allowing more children reduces the strengths of these considerations; however, psychosocial worries increase for donors and their families, and maybe also for the donor offspring. At much higher numbers of donor offspring (around 200) medical-genetic doubts arise, as may ethical doubts, depending on the point of view taken (i.e. should a donor child be considered to have a bond with his donor, or not). At offspring numbers around 200, legal issues also start playing a role, as explained in the section General considerations: the multiplied number of offspring cannot be higher than the collective number allowed by individual countries (with about 20 countries in the European Union and a mean national limit of 10 children per donor, the total number of offspring in the EU cannot become more than $20 \times 10 = 200$). As discussed below (recommendation 2), we believe that that these figures should be expressed in regulation as families and converted accordingly (using a family size of something like 2 children per family).

Not only do different viewpoints exist among the participants in donor insemination, which lead to different donor quota, specific viewpoints may also be more important for different

parties and work out differently for each. Moreover, different parties just may have different interests. A recommendation reached on the basis of viewpoints from one party may be devastating for the interests of another. It is far from clear how to weigh up all viewpoints comparatively, and even whether one point of view should outweigh another. In the absence of research evidence, many arguments are based on what seems reasonable, sensible, normal and responsible to those proposing them, whereas, to others, they may appear only ideas, intuitive guesses or otherwise subjective even if sincerely held.

Arriving at a definite quota necessitates a balance to be made between extreme, almost non-restricted activities that most people will consider irresponsible, versus regulated activities with standards so strict that the service will be unable to operate because of economic reasons and shortage of donor material.

We might abandon the setting of any quota in view of the lack of evidence and consensus, as some countries have done (Sweden, Canada) (Janssens *et al.*, 2011). The alternative is to recommend quota based on nothing more than reasonable sounding opinion, taking into account for better or worse the interests of all stakeholders. The latter, in different countries, has resulted in a wide variety of quota, apparently weighing up arguments and interests that are vastly divergent. Using this approach, the international working group of authors on this paper came to a consensus that the number of offspring created per donor internationally should be limited to not exceed 100 families (a number not based on medical evidence, calculated from the aforementioned figures assuming a family size of two children per family). The psychosocial professionals in our team, however, could only support a lower number (of around ten families). For use in a smaller area, e.g. a population of several millions living within a country or a district a lower figure than 100 families might be applied. The group were in total agreement that once a couple had a child a genetic-sibling pregnancy should not be precluded and hence the numbers are framed as such in a ‘family’ not ‘individual’ quota model. This was on the grounds of parental desire to minimize the levels of non-genetic relationships within their family, the wish children may have to be full-genetic siblings, and also ease of managing any subsequent contact with one donor rather than having to manage more than one should a different donor be used. Unfortunately only about one-half of the regulations and recommendations to date reflect this ‘family’ way of thinking (Janssens

et al., 2011), despite creation of a family being at the very core of this treatment modality. We strongly recommend that this should prospectively be the case.

Finally, the group reached a consensus that the patient choosing treatment with donor sperm always has the absolute right to understand what that treatment may mean for themselves or their child. As such, whatever quota is set by any bank or agency, the prospective parent should be provided a clear statement about what limit, if any, there is to the number of families that may be created with that donor in their country as well as internationally, and over what time duration that donor may be used in treatments over (e.g. 5 or 30 years). Sperm banks distributing gametes over different countries should be open over their policy in counting offspring and the limits they apply internationally. Indeed in some countries, this may well fall within the patient's legal rights 'to know' about their treatment. It seems impossible to argue against the rationale that the practice of donor supply works best for those being treated and their offspring when information on the exact potential 'family' numbers is disclosed.

The lowest, strictest limit in the number of offspring per donor, in fact in any donor insemination activities and regulations on assisted reproduction techniques, may be determined by the possibilities for individuals to escape the formal rules as the official institutions are (or will be, in case of international regulation) required to apply. For donor information sources, parents may turn to the Internet. Nowadays, more than ever, people can easily arrange their reproductive goals in private. The international platform is especially a place in which possibilities to escape the formal rules are available: people can obtain donated gametes from abroad, make arrangements with foreign institutions and travel to almost any country with cheap tickets. People can and do find their own way (Ernst *et al.*, 2007; Pennings *et al.*, 2008; Farraretti *et al.*, 2010; Shenfield *et al.*, 2011). These activities apparently are counterproductive to the wish in society to provide responsible health care. Worse even, a number of people will be harmed by impossibilities to fulfill their wish at home, either because they cannot afford the use of alternative ways for obtaining assisted reproduction techniques and donor gametes, because they fear to make use of non-official supply of gametes and stay childless, or, because they become victim of malevolent persons

active in the non-official circuit and will encounter inappropriate help or damage for themselves or their offspring's health.

It will be clear that the possibilities of supervising the activities of donor insemination in the non-official circuit are limited. Although this should not be used to justify the lack of any regulation or quota, it does support a system in which patients have the necessary choice safely available. It seems that we will have to live with a non-research-evidence based donor quota for a number of years still to come. Years with ongoing debate and news media highlighting exceptional cases and incidents may result in quests for stricter and far-reaching regulations, unrealistic (at least in the eyes of some) and potentially eroding the system as has occurred before (Boggio 2005; Pennings, 2012). We will have to accept cross-border reproductive care and individual initiatives in private. The best we can do is to provide guidance (i.e. be transparent and informative) and strive to prevent the negative consequences.

In summary, the general, genetic, psychosocial, operational and ethical considerations lead the working group to propose the following three recommendations: (i) the offspring number created per donor used internationally should be limited no more than 100 families. Consideration should be given to the arguments of the psychosocial professionals who suggest numbers nearer to 10; (ii) calculation in donor insemination should be per families, as should recommendations on acceptable numbers of offspring per donor, rather than in individual offspring, wherever possible. This enables optimal possibilities for parents to have children from the same donor; (iii) prospective parents should be provided clear information on the limits, if any, of families or offspring that may be created by a donor and the duration of time over which donations from a given donor will be offered to others for treatment; sperm banks should be open over their policy in distributing gametes and counting offspring applied in the international sphere.

It will be clear that with these recommendations no unifying agreed limit or straightforward conclusion is presented. Rather, the recommendations provide minimum standards for responsible international use of donor sperm, to be used as support and guidance.

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Declaration

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Figure 1: Donor quota: what occurs when gametes are internationally used, within the constraints set by national regulations and laws.

Green colour: no compulsory rules. Advice: limits used should come from other arguments (e.g. as formulated by the working group [present paper]).

Orange colour: operation has to be according to limits expressed by the national regulations and laws (adopting the most stringent rule of either).

Limits only expressed for donors applied abroad and limits only expressed for donors from abroad, if existent in any country, have not been incorporated in the table.

Figure 2. The different recommendations on the maximal offspring number per donor, reached by considering the issue from various perspectives. The ordinate of this figure has no numbers as it does not represent concrete data.

Considerations and effects as related to: —•—genetics, —••—••psycho-social, — — ethics, ●●● operation of DI, — donor availability, = = = legal issues.

Table 1. Comparison of characteristics of use of donor gametes on national and international scale

<i>Issue</i>	<i>relevance for questions on donorquota</i>	<i>National use</i>
Area of distribution	Potentially affects the number of recipients that can be helped in total, enabling also to obtain less donor offspring in comparison to non-donor offspring ('dilution effect').	Use in a restricted area.
Geographic convenience	Affects the choices recipients make, with possible effect on concentration in certain countries and centres.	Affects which centres recipients go to in a country; multiple choices often at a distance.
information available about treatment possibilities (word of mouth, Internet, other)	Affects choices recipients make, with possible effects on concentration of facilities in certain countries and centres.	Affects which centres recipients go to in a country; local contacts between people knowing each other may be influential.
Treatment options for married and heterosexual, lesbian or singles	Affects international traffic of gametes (provided by suppliers) or recipients and offspring numbers of donors in supplying centres and countries.	Less or more restricted choice, depending on national regulation and laws.
Anonymity of donors	Determines possible contact of offspring with donor and possible psychological burden which (high numbers of) offspring may form for donors.	Whether or not anonymous are allowed varies, depending on national guidelines.
Genetic risk of inbreeding (comparing the same number of donor offspring per donor).	Increasing offspring numbers result in increased chances of unwitting relations between half siblings (consanguineous relationships).	Present, although small at a certain level of offspring per donor (e.g. 25 per donor).
Risk related to monogenetic diseases in donor offspring.	Increasing offspring numbers lead to higher chance that offspring with accidental genetic diseases are encountered.	Low when national quota are low, but higher in the case and even lower when genetic screening of donors is applied (not standard).
Number of offspring per donor.	The ultimate question dealt with by the working group and in the present contribution.	Determined by national regulation and what is available,
Way of counting offspring allowed per donor (donor quota).	Distinguishing counting individual donor offspring or families helped with gametes from one donor lead to different outcome.	Uniform within countries, as determined by national regulation, if available
Feedback to authorities, semen bank, or both, by recipients about pregnancies and deliveries obtained	Determines the extent to which accepted or compulsory donor quota are consequently applied and can be trusted.	May be complete, depending on the system in operation, its supervision and management.
Data registration on pregnancies and deliveries (by authorities, semen bank, or both)	Determines the extent to which accepted or compulsory donor quota can be supervised, probably affecting the extent to which they are actually applied.	May be (almost) complete, depending on the system in operation, its supervision and management.

Quality and safety of help.

Relates to the extent that directors and professionals are willing to apply responsible donor quota, supervise and control (the number of) offspring per donor. Affects a.o. (AUTHOR: PLEASE WRITE OUT a.o. IN FULL) the information given to recipients in case of casualties or donor is found to have genetic diseases (limiting the use of them). May indirectly affect the choices recipients make.

Rather uniform within countries, countries variable. Level depending system and supervision. Locals can obtain rather good idea of it.

Patient involvement.

Affects the choices for centres recipients make, with possible effects on concentration of them to certain countries and centres.

Absence of language barriers may recipients choice to start and continue

Table 2: Risks for consanguineous relationships among donor offspring, calculated for a population of 200,000 inhabitants with 1250 donor children per year, equally distributed among heterosexual, homosexual, families and single mothers, in an open-identity system.

<i>Number of children per donor</i>	<i>Chance of a consanguineous relationship for a donor child (%)</i>	<i>Expected number consanguineous relationships for a population of 16×10^6</i>
10	0.011	0.022
25	0.026	0.054
50	0.051	0.106
100	0.101	0.210
200	0.201	0.418

It is assumed that all donor children in homosexual families and from single mothers know their donor-fathers, and that one-half of the donor children in heterosexual families know their donor-fathers and that maximal age difference between partners (with diminishing probability) is 5 years.

Author biography

Pim Janssens is a senior clinical (bio) chemist. He studied biochemistry in Amsterdam, obtained a PhD in science, and went on to train as a clinical (bio)chemist. He is specialized in inborn errors of metabolism. He was laboratory director for 6 years, with an interest in exploring the professional, organizational and ethical aspects of gamete donation. Pim Janssens has been the chairman of the Dutch Society of Semen Banks for more than 10 years, and has published articles on gamete donation, laboratory organization, test ordering management and risk assessment.

Comment [S3]: Author: please name laboratory

Comment [S4]: Author: articles ok? Or books as well?

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