BELGIAN ADVISORY COMMITTEE ON Bioethics

Opinion no. 62 of 12 October 2015 on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial

Content of the opinion

Request for an opinion

On 21 June 2011, Prof. André Herchuelz, in his function as chairperson of the Medical Ethics Committee of the university hospital Erasmus and the Université Libre de Bruxelles, made a request for an opinion of the Advisory Committee for Bio-ethics on "the 'statute' of the pregnant partner of a male participant in a clinical trial and the ethical implications of that statute."

The situtation concerned was as follows (translated from the original request made in French):

> "It can happen that drugs that are the subject of clinial trials are potentially toxic for gametes or foetuses, with possible consequences for any offspring conceived during the trial. Our request for an opinion focuses on the specific case in which toxicity is caused by the sperm of a male participant, or the toxicity affects the gametes of a male participant. In this particular case, the researchers who are responsible for the clinical trial ask the medical ethics committee for permission to collect data regarding the further development of the pregnancy and the growth of the child.
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> We agree to this request to collect data coming from the pharmaceutical company sponsoring the clinical trial, on condition that the pregnant partner completes an informed consent document. This informed consent document needs to clearly state the reasons for this "pregnancy monitoring programme" and must point out to the signatories their rights in the framework of this "monitoring programme". Under rights we understand the confidentiality of the collected data, the right to a contact person in case of a problem or any form of concern on their part, and the right to withdraw their consent at any time without being put under pressure of any sort.
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> In general, this kind of informed consent document is able to be obtained with varying degrees of ease, depending on the company.
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> We are however systematically faced with the refusal to consider these pregnant women as participants in the clinical trial, on the grounds that they themselves are not ingesting the drug being trialed and that the participant was sufficiently informed of the risks involved with conceiving during the study (transmission of the drug being tested via the sperm, the genotoxic effect of the drug on the spermatocytes) and of the contraceptive measures that should be taken.
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> The refusal to consider female partners who become pregnant during the trial as participants in the clinical trial starting from the moment that they sign an informed consent document, has ethical implications, as these female partners are then unable to enjoy the rights granted to participants of experiments on the human person (Law of May 2004).
>
> The companies justify this refusal by stating that they are not liable for any harm caused to the prengant woman or the unborn child, even if this harm is in any way related to the participation of the male partner in the clinical trial.
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> This argumentation is based on the liability of the parents who, knowing the risks, decided to initiate a pregnancy […].

From an ethical point of view, the Medical Ethics Committee of the university hospital Erasmus and the Université Libre de Bruxelles considers it to be justified that participants in clinical trials be required to respect a certain number of conditions regarding responsible sexual behaviour. This responsibility lies chiefly with the participant of the clinical trial, as the one who signs an informed consent document before participating in the trial.

However, the Committee considers it to be unethical for companies to inform pregnant women that the company is in no way liable for any harm caused to the woman or her as yet unborn child. This position of the Committee is supported by the fact that conception can occur as a result of sexual relations (possibly in the absence of a committed relationship) with a partner who fails to inform the woman of possible risks for her potential offspring. In the light of this, it is important to consider that an effective utilisation of contraception needs to take into account both the male participant in the trial and his female partner(s). This means that it is very difficult to be able to state with certainty that all those involved can sufficiently appreciate the risks for their potential offspring caused by ingestion of the drug being trialed.

Stating this more generally, the ethical issue here is whether either of the parents as individuals, or the child conceived during the clinical trial, can be held <u>solely</u> liable/responsible[1] for the adverse consequences of the tested product, simply due to the fact that the participant was informed by the researcher of the risks for the child.

It should not be forgotten that sexuality also includes a range of emotional aspects which influence behaviour and decisions, and that the idea of conception risks during the trial phase will be theoretical and indirect for the participant who is informed of the risks. The risks are theoretical because there are in general no or little data available on the teratogenicity of the trial product, and they are indirect because the probability of pregnancy in cases of insufficiently protected sex is not well known, especially by the partners involved."

The plenary gathering of the Committee of 12 December 2011 declared the request to be admissable and referred it to the select committee 2010-1 "Clinical research." At the start of the fifth term of the Committee (8 September 2014), the request was referred to the select committee 2014-2 "Experiments on the human person", who prepared this opinion.

The Committee made inquires[2] to seven Belgian university hospitals regarding the occurrence of a problematic pregnancy of the partner of a male participant in a clinical trial. Responses from four university hospitals were received, and none had come across a problematic pregnancy of this kind.

1 In the original French text, the words used are "portent-ils seuls la responsabilité". The concept "responsabilité" has both legal and ethical dimensions, which we have translated here as "liable" and "responsible" respectively. Both dimensions – legal liability and moral responsibility – are discussed in the current opinion.

2 The following question was asked in May 2012: *"The members of the Committee wish to inquire of the university obsterics departments whether they have ever come across cases in which a woman had problems (or was concerned) during or after a pregnancy during which her partner had participated or was participating in a clinical trial of a potentially toxic drug."*

In practice, it is difficult to establish a link between a product and a foetal anomaly or congenital defect given that the general or "natural" risk is limited. Furthermore, the effect of a toxic product generally leads to the destruction of the male participant's spermatozoa. Any connection between a toxic effect of the product in the (pregnant) woman and a defect in her child will usually only be discovered by coincidence.[3] In the past, the adverse effects of pregnant women ingesting thalidomide for their unborn children were only discovered because a number of babies were born with missing or underdeveloped limbs at the same time as the clinical trial, and this is a very rare defect.

This may seem to be a case of an extremely limited medical risk, but if it were to occur, there could be real adverse consequences.

In what follows, we first discuss why it is impossible to exclude the possibility of a problem occuring, and then sketch the biological model.

1. Product of the trial

The medical product to be tested on the male participant can:

(1) belong to a class of drugs with known genotoxic, teratogenic or embryotoxic effects,[4] or
(2) remain in the body for an extended period of time so that even after the completion of the trial, the product is still present in the man's body at the moment of conception, or
(3) in the case of an authorised drug, have a warning regarding potential risks for conception included in its Summary of Product Characteristics (SPC or SmPC, formerly known as the Data Sheet).

The example of Ribavirine

The SPC for Ribavirine – a drug used by chronic Hepatitis C patients and by children infected with the respiratory syncytial virus – includes the section "4.6. Fertility, pregnancy and breastfeeding", in which the following is stated:

> "Male patients and their female partners: everything should be done to avoid a pregnancy for the partners of male patients who take Ribavirine [...]. Ribavirine

3 A biomedical experiment involving potential drugs involves a number of subsequent phases. This type of experiment begins with laboratory trials, which aim to study the fate and effects of the drug in living organisms. Laboratory trials include the following phases:
- first on body cells;
- then on small rodents such as mice or rats;
- subsequently on dogs or cats;
- and in the case of possible side effects on embryos, also on primates

Experimentation on humans is only commenced once all these studies (*in vitro*, and *in vivo* on animals) have provided favourable results. Even then, the possibility can never be excluded that adverse effects might be observed for the first time during the first human trial.
Following the laboratory trials, clinical research is conducted in four phases. In phase 1 the drug is administered for the first time to humans. In principle this will be a small group of healthy volunteers. The aim of phase 1 is to test their tolerance for the product, to determine the maximum dosage that can be tolerated and the minimum effective dosage, and to study the pharmacokinetic and pharmacodynamic properties of the drug.
For more information please refer to the introductory report of opinion 13 of 9 July 2001 of the Belgian Advisory Committee for Bio-ethics on experiments on the human person.

4 Genotoxic refers to harm caused to the DNA leading to mutations or cancer
Teratogenic refers to disruption to the tissue development of the unborn child caused by a chemical (e.g. thalidomide), physical (e.g. radiation) or other substance, leading to congenital defects
Embryotoxic refers to toxic substances that poison the already existing embryo.

accumulates in the cells and is eliminated very slowly from the body. It is unknown whether Ribavirine present in sperm can have teratogenic or genotoxic effects on the embryo or foetus. Although 300 prospectively followed pregnancies in which the father was treated with Ribavirine did not indicate a higher risk of malformations than in the general population or a specific pattern of malformations, male patients and their female partners of fertile age should be advised to both use an effective contraceptive during treatment with Ribavirine [...] and for seven months following the completion of treatment. Men whose partners are already pregnant should be required to use a condom to reduce their partner's exposure to Ribavirine during sexual intercourse."

2. The biological model

The very small medical risk is connected to the possibility of genotoxicity, teratogenicity and embryotoxicity.

Two types of medical risks should be distinguished:

- the possibility of harm to the gonads of the male participant through genotoxicity;
- the possibility that the product of the trial affects the unborn child via the sperm released during sexual intercourse

Firstly, there is the possibility of genotoxicity. If the drug being tested only has potential consequences for the spermatozoa, then there is no danger for a woman who was already pregnant before the commencement of the clinical trial, as conception has already taken place.

Regarding the potential consequences for the spermatozoa, the moment of conception and the sperm maturation cycle need to be taken into account. There are 100 days between the appearance of the primitive spermatozoon cell (the spermatogonium) and what is ejaculated. This 100 days is based on the 74 days (with a standard deviation of ± 4 days) of development between the spermatogonia and the mature spermatozoa,[5] plus the transit time through the epididymis of 12 to 21 days.[6] The sum of the maximum terms equals 99 days, which is rounded up to 100 days. On the basis of this number, a genotoxic effect occuring during the three months prior to conception could raise problems. At the same time, it should be noted that such effects will usually occur in an early stage of spermatozoa development, rather than in a later stage.

A second possibility is that small amounts of the test product will reach the unborn child via the sperm released during sexual intercourse. If it is possible for the drug being tested to contaminate

the spermal plasma in this way, then there remains a risk for the woman (and the child) during pregnancy. As a comparision, women can also be infected during pregnancy by the HIV-virus originating in spermal plasma.

5 Heller C.G. en Clermont Y, Spermatogenesis in man : an estimation of its duration, *Science*, 1963, 140, 184-186.
6 Rowley M.J., Teshina F., Heller C.G., Duration of transit of spermatozoa through the human male ductular system, *Fert. Ster.* 1970, 21, 390-396.

Legal and Ethical Considerations

We take as starting point a clinical trial in which the test product could present a very small medical risk which could, if the risk becomes reality, lead to adverse consequences.

1. A thorough and adequate informed consent process

The Committee members emphasise the importance of a thorough and adequate informed consent process.[7] The participants or their legal representatives[8] must be informed in writing and in advance regarding at the least the experiment's nature, scope, objectives, consequences, expected benefits, risks, and context, plus the identity and the opinion of the authorised medical ethics committee, and the right of participants to withdraw themselves from the trial at any time without the risk of any disadvantages.[9]

A signed informed consent document is necessary[10] but does not in itself count as conclusive evidence of a well conducted and adequate informed consent process. One should be able to expect after conducting a thorough informed consent process that the participants understand well the aim, risks and conditions for participation in the study.

In particular, the members of the Committee point to the duty to inform the male participant in a complete, clear and understandable manner regarding the potential medical risk of the test product for the participant himself as well as his partner(s) and his offspring. This applies especially in the case of first-in-human trials or phase 1 trials, in which the product is tested on humans for the first time. In this regard, particular attention should be given in the first place to risks for partners who are already pregnant before the commencement of the clinical trial, and then also to risks for partners who become pregnant during the course of the trial or even a certain amount of time after the last ingestion of the test product, as well as risks for the unborn child.

In the case of a possible risk of contamination of the sperm, the test product can also reach the partner and the unborn child through unprotected sexual intercourse. The participant must therefore be well informed about the possible risks for a partner who is already pregnant before the commencement of the clinical trial, as well as for a partner who becomes pregnant either during the course of the clinical trial or during a certain amount of time after the last ingestion of the test product.

The participant must also be informed of the duration of the period after the last ingestion of the

7 Article 6 of the Law of 7 May 2004 on experiments on the human person. See also article 9 of regulation number 536/2014 of 16 April 2014 (which will enter into force from 28 May 2016 at the earliest).

8 Article 7 and article 8 of the Law of 7 May 2004.

9 Article 6 § 2 of the Law of 7 May 2004.

10 Article 6 § 1 of the Law of 7 May 2014; under this provision, someone who participates in an experiment who is unable to give their consent in writing can do this verbally in the presence of at least one adult witness; this witness must be independent of the sponsor of the trial and the researcher.

test product during which there still exists a potential (albeit minimal) medical risk of adverse consequences. In the case of a potential risk of genotoxicity, the participant must thus be very well informed as to the period of 100 days to be counted starting from the last ingestion of the test product. As a precaution, this period that the participant should take into account should include a safety margin.

In cases in which the condition of not initiating pregnancy is imposed on the participant, the necessary counselling should also be provided regarding the possible risks associated with not complying with the terms of the protocol, regarding the protection measures to be taken during sexual intercourse, i.e. the use of double contraception,[11] condoms should be offered, and a contact person should be designated (e.g. to give advice in case the participant has unprotected sexual intercourse, or if the participant leaves the study prematurely to reinform him of the remaining possible risks and the precautionary measures that should be taken).

2. Two distinct studies

The Committee members are of the opinion that clinical trials involving healthy male volunteers and observational studies involving pregnant women and their unborn children are two distinct types of studies. The (potentially already) pregnant woman and the unborn child do not belong to the inclusion group of clinical trials. It would be difficult for a clinical phase 1 trial in which a drug is tested on healthy male volunteers to include at the same time a follow-up of pregnancies, as this would amount to accepting that the foetuses be exposed to risks.

If a pregnancy were to arise, the sponsor of the clinical phase 1 trial should generally be interested in investigating the possible effects of the test product (moral responsibility). Even if the sponsor were not to set up an observational study, this would not prohibit anyone else taking the initiative to collect and investigate data on the course of the pregnancy. This would then be an observational study with the woman as participant, for which the Law of 7 May 2004 on experiments on the human person is also applicable. This implies the necessity of a thorough and adequate informed consent process and the taking out of a no-fault liability insurance for the participant. However, any harm or adverse effects that the pregnant woman might undergo as a result of the ingestion of the test product by her partner, are to be considered the result of the clinical phase 1 trial and not the result of the observational study. This is harm or the possibility of harm that existed before the start of the observational study, which is not covered under the obligation to take out a no-fault liability insurance in the context of the observational study.

3. Liability for the harm caused as a result of ingesting the trial product

The no-fault liability insurance in the context of the clinical trial only covers harm caused to the participant. It includes harm linked either directly or indirectly to the experiment. Article 29 § 1 of the Law of 7 May 2004 on experiments on the human person states in this regard: "*The sponsor*

11 Double contraception provides a double level of protection through the use of a spiral or the pill to prevent pregnancy, combined with a condom.

assumes, even without fault, liability for the damage which the subject and/or his rightful claimants sustained and which shows either a direct or indirect connection with the trial; every contractual provision aiming at limiting this liability is considered null."

The participant can undergo indirect harm as a result of ingesting the test product because of, for example, the need for special care for the child because of harm caused to the child, or because of moral harm suffered by him as a result of harm caused to his female partner or the child.

If, however, it is a matter of thorough and adequate informed consent and the participant breaks the terms of the clinical trial regarding the prohibition of initiating pregnancy or the use of double contraception during sexual intercourse, and instead the participant causes a pregnancy, this could make him liable.

Niether the pregnant woman nor the unborn child[12] can be considered as participants in the clinical trial, meaning that the obligation to take out a no-fault liability insurance does not apply to them. The concept "participant"[13] should be understood in a narrow sense. The pregnant woman and the child born with a disability may, if they so desire, bring a liability claim for damages before the courts.

4. Ethical issues

The Committee stresses the importance of good protection for the trial subjects. In the interests of the trial subject, it is primarily the responsibility of the sponsor to limit the risks of the research to a minimum. The medical ethics committee responsible for providing an opinion on the research should examine this issue. Moreover, the Committee emphasises the importance of a quality informed consent process. In this regard, attention should be paid to the fact that trial subjects often have difficulty understanding, processing, and remembering information. The new European Regulation (EU Regulation Number 536/2014 of the European Parliament and of the the Council, which comes into effect in 2016) states the following requirement in this context:

> "Information given to the subject... for the purposes of obtaining his or her informed consent shall... (b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson; (c) be provided..."

The Committee is of the opinion that the process of informed consent must explicitly mention the following elements:

- That the period of risk stretches from the start of the clinical trial (first ingestion of the test product) up until and including 100 days after the last ingestion of the test product;
- That the pregnancy of the partner or a refusal to use double contraception are considered to be exclusion criteria; in other words, attention must be given to the importance of (1) the partner not becoming pregnant during the course of the clinical trial and (2) the partner

12 See the definition of "human person" according to the Law of 7 May 2004 on experiments on the human person, article 2, 23°: "a born, living and viable person."
13 See the definition of "participant" in article 2, 20°: "an individual who participates in an experiment, regardless of whether they belong to the experimental group or the control group."

not being pregnant at the moment of inclusion (of the male partner) in the clinical trial;
- That if the partner does become pregnant, the participant is requested to take contact with the researcher as soon as possible;
- That the participant is encouraged to inform his partner(s) about his participation in a clinical trial or drug experiment; and that the sponsor of the clinical trial formally declares to be prepared to answer the questions of the participant's partner(s);
- That the participant declares that he will not act as sperm donor from the start of the clinical trial up until and including 100 days after the last ingestion of the test product.

According to the Committee, caution should be exercised in assessing the degree of shared responsibility on the part of the trial subject in the prevention of a possible pregnancy. Although the trial subject initially commits to respecting the conditions of participation in the clinical trial, he cannot simply be held responsible for a possible violation of these conditions without further ado. Notwithstanding the *moral responsibility* of trial subjects to respect the conditions of participation in a trial and to inform their partner about their participation, they remain vulnerable, not least in such an emotional area as sexuality. For this reason, the responsibility for risks cannot be simply and unambiguously attributed to the trial subject, even when he violates certain conditions of participation. An additional complexity is that while trial subjects have the right to stop their participation in the trial at any time, the risk of harm continues for an extra 100 days after this decision is made.

Recommendations

The Committee unanimously recommends the following:

Firstly, the Committee notes that a clinical trial (an interventional drug study) in which a male trial subject participates is distinct from an observational study set up in the case of pregnancy of the participant's partner (a follow-up study of the effects of the pregnancy). These are two distinct studies, both of which fall under the scope of the Law of 7 May 2004 on experiments on the human person. The possible risk for the pregnant woman and her unborn child as a consequence of the participation of the woman's partner in a clinical trial, is a risk that is not covered by the no-fault liability insurance in the context of the original clinical trial.

The Committee points to the importance of a thorough and timely informed consent process. In particular, the sponsor must inform the participants or their representatives in writing that the test product could be harmful for the participant himself as well as for his partner(s) and for any potential children conceived during the risk period.

More specifically, the Committee recommends that the following elements be included in the consent document:
- That the period of risk stretches from the start of the clinical trial (first ingestion of the test product) up until and including 100 days after the last ingestion of the test product [see explanation under section 2. The biological model];

- That the pregnancy of the partner or a refusal to use double contraception are considered to be exclusion criteria;
- That if the partner does become pregnant, the participant is requested to take contact with the researcher as soon as possible;
- That the participant is encouraged to inform his partner(s) about his participation in a clinical trial or drug experiment; and that the sponsor of the clinical trial formally declares to be prepared to answer the questions of the participant's partner(s);
- That the participant declares that he will not act as sperm donor from the start of the clinical trial up until and including 100 days after the last ingestion of the test product.

The opinion was prepared by select commission 2014/2, consisting of:

Joint chairpersons	Joint reporters	Members	Member of the Bureau
Evelyne Langenaken	Steven Lierman	Wim Distelmans	Paul Schotsmans
Robert Rubens	Wim Pinxten	André Herchuelz	
		Julien Libbrecht	
		Jacques Machiels	
		Robert Nailis	
		Virginie Pirard	
		Stany Wens	

Member of the secretariat
Veerle Weltens and Francine Malotaux

The working documents of the select commission - the question, personal contributions of the members, minutes of the meetings, documents consulted - are kept on file at the Committee's Documentation Centre where they are available to be consulted and copied.

This opinion is available to be consulted at www.health.belgium.be/bioeth

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