Health Canada Santé Canada

Assisted Human Reproduction Implementation Office

Consultation Background Paper
Conduct of Controlled Activities under the *Assisted Human Reproduction Act*

Fall 2006 Consultations

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Canada

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Consultation Background Paper on the Conduct of Controlled Activities

1. Introduction

The *Assisted Human Reproduction Act* (the Act) governs the practice of assisted reproduction and related research. The Act has three objectives: to prohibit unacceptable practices, to address the health and safety of Canadians using assisted human reproduction (AHR) to help build their families and to require that research involving *in vitro* human embryos takes place in a controlled environment.

The Act defines "assisted reproduction procedure" as "any controlled activity referred to in section 10 that is performed for the purpose of creating a human being" (section 3). According to the Act, "controlled activity means an activity that may not be undertaken except in accordance with sections 10 to 12". Specifically, section 10 of the Act states:

10(1). No person shall, except in accordance with the regulations and a licence, alter, manipulate or treat any human reproductive material for the purpose of creating an embryo.
10(2). No person shall, except in accordance with the regulations and a licence, alter, manipulate, treat or make any use of an *in vitro* embryo.
10(3). No person shall, except in accordance with the regulations and a licence, obtain, store, transfer, destroy, import or export
(a) a sperm or ovum, or any part of one, for the purpose of creating an embryo; or
(b) an *in vitro* embryo for any purpose.

In late February 2006, AHRIO consulted stakeholders on licensing for AHR procedures. At that meeting, participants discussed a list of controlled activities. At present, we are developing a regulatory framework for the controlled activities involved in the basic *in vitro* fertilization (IVF) process.

The aim of this consultation is to seek input and to discuss the control measures in regards to mitigating the risks associated with the following controlled activities for persons using their own gametes for their own reproductive use: 1) semen/sperm obtaining, 2) clinically retrieving sperm, 3) semen/sperm processing, 4) controlled ovarian hyperstimulation, 5) oocyte[1] retrieval, 6) oocyte processing, 7) IVF with insemination (conventional IVF), 8) IVF with intracytoplasmic sperm injection (ICSI), 9) *in vitro* embryo culture and assessment, and 10) *in vitro* embryo transfer.

1 To ensure consistency with the scientific literature, the term oocyte has been used in this consultation paper and related documents rather than the term ovum which is used in the Act. Oocyte, as used throughout this document, has the same meaning as the term ovum as defined in the Act to mean "a human ovum, whether mature or not".

2. Policy instruments to mitigate risks related to the conduct of controlled activities

There are various policy instruments that can be used to mitigate risks associated with controlled activities such as:

- guidelines;
- regulations;
- standards or professional guidelines incorporated by reference in regulations[2]; and
- terms and conditions of controlled activities licences.

At this time, Health Canada seeks input on the inclusiveness of the various proposed control measures and the contributing factors that may give rise to negative outcomes associated with AHR procedures as listed in Appendix B. The choice of policy instrument will be determined at a later date.

The Act authorizes the creation of regulations that will establish requirements for the undertaking of controlled activities. Some of the proposed control measures in Appendix B are written in general terms, and we will be seeking input in order to make these proposals more precise and clear. The next steps will include making decisions on the implementation of control measures in the regulations, either directly or through incorporation by reference of existing guidelines.

3. Health and Safety Risks and the Proposed Control Measures for Controlled Activities

Risk is used by persons to refer to a variety of different issues in AHR. Risks can be 'theoretical' in nature, or 'real' based on scientific evidence from studies conducted on animals or humans. The quality and quantity of evidence available on risks in AHR varies considerably. This document discusses risks that may lead to negative outcomes to the potential child and to persons undergoing AHR. An example of 'real' health and safety risks to women undergoing AHR would be ovarian hyperstimulation syndrome (OHSS) whereas the imprinting defects in the offspring would be an example of a risk that is not fully scientifically proven. Risk can also be used to refer to the possibility of a mistake that occurs through human error such as the risk of misidentification of a sample or the improper conduct of a procedure (see Appendix A).

Our analyses of the health and safety risks associated with the conduct of each controlled

2 The technique of incorporation by reference is used to incorporate the requirements set out in a document into the regulations, without actually having to reproduce the text in the regulations. The effect is that the incorporated text becomes part of the regulation.

activity and the control measures used to mitigate conduct risks were determined through extensive literature research and analysis and through analyses of numerous national and international standards, practice guidelines and codes of practice (see Appendix C).

Control measures to mitigate risks can be characterized as general, which apply universally to all AHR procedures (e.g., control measures mitigating the risk of misidentification and contamination), and specific, which apply to the individual controlled activities. The tables presented in Appendix B refer to both general and specific control measures.

It should be emphasized that the list of control measures (Appendix B) for the conduct of controlled activities is presented as a point of commencement for discussion at these consultations and is not intended to be exhaustive and final. Based on the present consultations and the initial stakeholders' input, Health Canada will be further analyzing policies in order to propose regulatory requirements.

Appendix A

Negative Outcomes Related to Controlled Activities

Negative outcomes	Causes	Occurrences
Reduction of reproductive capacity / potential, i.e., loss of gametes or *in vitro* embryos	due to: • damaged gametes or *in vitro* embryos (improper materials, reagents, temperature, pH, osmolarity, contamination) • misidentification • improper records • improper assessment	during gamete and *in vitro* embryo handling
Harm to persons undergoing AHR	clinical risks, e.g., surgical risks, infection, OHSS	surgical sperm retrieval, oocyte retrieval, *in vitro* embryo transfer
Harm to offspring, e.g., congenital malformations, imprinting disorders	due to: • damaged gametes or *in vitro* embryos (improper materials, reagents, temperature, pH, osmolarity, contamination) • improper assessment	during gamete and *in vitro* embryo handling
Birth of a child with an unintended genetic parentage	due to: • misidentification, e.g., mislabelling of samples • improper records • lack of "double-checking" the identity of patients, gametes and *in vitro* embryos	during gamete and *in vitro* embryo handling

Appendix B

Health Canada reviewed requirements of national and international guidelines, standards and codes of practice established by and for the AHR sector. These touch on various components of good laboratory practices (GLPs) and good clinical practices and the elements of quality assurance programs. GLPs include standard operating procedures, isolation of activities that require sterile techniques and monitoring the quality of services provided by outside sources. Some of the requirements reviewed are beyond the scope of the Act, such as those relating to occupational health and safety. Others are written in a level of specificity or make requirements that are beyond our objective to mitigate health and safety risks. For example, some have administrative and information requirements beyond that needed to meet an appropriate level of protection. The control measures proposed in the following table were derived from this review to address the health and safety issues identified.

Contributing Factors and Control Measures Related to Controlled Activities

Semen/Sperm Obtaining: Self-collection

Contributing Factors	Proposed Control Measures
Contamination of the sample	- Use of a sterile container
Environmental factors that affect sperm quality	Instructions provided to the donor should specify: - not to use condoms, creams or lubricants - abstinence from ejaculation of 2-5 days prior to collection - temperature maintenance - prompt delivery to the clinic
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
Improper Records	- Records should be kept indicating each and every occasion when gametes are handled, and by whom
	Records should include: - patient identification - method of collection - period of abstinence

	- type of container used - time and place of collection - whether any collection or transport problems occurred

Clinically Retrieving Sperm

Contributing Factors	Proposed Control Measures
Contamination of the sample	- Surgical procedure performed by a qualified person[3] - Use of aseptic techniques
Surgical Risks e.g., tissue damage, infection, anesthetic risks	- Surgical procedure performed by a qualified person
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
Improper Records	- Records should be kept indicating each and every occasion when gametes are handled, and by whom
	Records should include: - the name of practitioner - the pre-operative diagnosis leading to the procedure - the procedure used - type of anesthesia given - the name and dosage of any medications given - patient identification - date of collection - whether any collection or transport problems occurred

3 The licensing of qualified persons to undertake controlled activities is the subject of a separate document.

Semen/Sperm Processing

Contributing Factors	Proposed Control Measures
Use of inappropriate preparation methods	- Gametes should be handled in a manner which protects their quality (e.g., using a method of preparation tailored to the individual sample, avoiding excessive centrifugation)
	- Written procedures for semen/sperm processing should be in place - Requirements should address that the processing of gametes is performed using sterile technique (while minimising the risk of contamination and cross-contamination between samples)
	- Procedure performed by a qualified person
Use of inappropriate equipment and materials	- If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity
	- Appropriate equipment for the purpose intended, the volume and the type of procedures performed - The equipment should be clean and disinfected
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
Improper Records	- Records should be kept indicating each and every occasion when gametes are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of gametes, such as serial numbers/batch numbers of equipment and materials coming into direct contact with gametes or data related to monitoring and maintaining

	the required conditions
	Records should also include: - patient identification - method of sperm preparation - sperm parameters before and after processing - date of processing - whether any problems occurred during processing (adverse events)

Controlled Ovarian Hyperstimulation (COH)

Contributing Factors	Proposed Control Measures
Use of inappropriate stimulation protocols and monitoring	- Procedure performed by a qualified person - Written procedures for COH should be in place - Having protocols for prevention, diagnosis and management of OHSS (requirements should include: ultrasound follicular tracking as an integral part of monitoring; women undergoing treatment with clomifene citrate should be offered ultrasound monitoring during at least the first treatment cycle) - The use of ovarian stimulation agents should be confined to the lowest effective dose and duration of use
Improper Records	Records should also include: - name of practitioner - patient identification - the fertility drugs used - doses and duration of administration - date of start of cycle - whether any problems occurred (adverse events)

Oocyte Retrieval

Contributing Factors	Proposed Control Measures
Contamination of the sample	- Surgical procedure done by a qualified person - Use of aseptic techniques
Surgical Risks e.g., bleeding, infection, internal organ damage, anesthetic risks	- Surgical procedure done by a qualified person - Protocols for oocyte retrieval may include the following requirements: • Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation • Women who have developed at least three follicles before oocyte retrieval should not be offered follicular flushing
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
Improper Records	- Records should be kept indicating each and every occasion when gametes are handled, and by whom
	Records should also include: - patient identification - the name of practitioner - oocyte retrieval method applied - number of follicles aspirated - type of anesthesia given - the name and dosage of any medications given - date of retrieval - whether any collection problems occurred (e.g., adverse events)

Oocyte Processing

Contributing Factors	Proposed Control Measures
Improper assessment	- Procedure performed by a qualified person - Written procedures for oocyte assessment should be in place
Inappropriate processing	- Written procedures for oocyte processing should be in place - Gametes should be handled in a manner which protects their quality (e.g., the rapidity with which each sample must be evaluated) - Requirements should address that the processing of gametes is performed using sterile technique
Use of inappropriate equipment and materials	- If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity
	- Appropriate equipment for the purpose intended, the volume and the type of procedures performed - The equipment should be clean and disinfected
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
	- Have suitable procedures in place to double-check the identification of gametes
Improper Records	- Records should be kept indicating each and every occasion when gametes are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of gametes, such as serial numbers/batch numbers of equipment and materials coming into direct contact with gametes or data related to monitoring and maintaining the required conditions

	Records should also include: - patient identification - number of oocytes retrieved - morphology (quality) of each oocyte - date and time of processing - whether any problems occurred during processing (adverse events)

In vitro Fertilization

Contributing Factors	Proposed Control Measures
Improper insemination procedure	- Procedure performed by a qualified person - Written procedures for insemination should be in place - Amongst other criteria, requirements should address: • the concentration of sperm used • avoiding reinsemination of unfertilized oocytes - Gametes and *in vitro* embryos should be handled in a manner which protects their quality - Written procedures that address processing of gametes and *in vitro* embryos should be performed using sterile technique
Use of inappropriate equipment and materials	If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity
	- Appropriate equipment for the purpose intended, the volume and the type of procedures performed - The equipment should be clean and disinfected
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
	- Have suitable procedures in place to double-check the identification of gametes
Improper Records	- Records should be kept indicating each and every occasion when gametes and *in vitro* embryos are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of gametes and *in vitro* embryos, such as serial numbers/batch numbers of equipment and

	materials coming into direct contact with gametes and *in vitro* embryos or data related to monitoring and maintaining the required conditions
	Records should also include: - Patients identification - The relative time for insemination (incubation time) - The concentration of sperm used for insemination - Number of oocytes inseminated - Date and time of insemination procedure - Whether any problems occurred during the procedure (adverse events)

Intracytoplasmic Sperm Injection

Contributing Factors	Proposed Control Measures
Unjustified use of ICSI	- Written procedure for ICSI should be in place - Requirements should address the circumstances under which ICSI may be applied such as: • In the presence of severe male infertility • Where prior fertilization failure or low fertilization by conventional IVF has occurred • When sperm was cryopreserved prior to cancer treatment • Prior to preimplantation genetic diagnosis for single gene defects performed by polymerase chain reaction. - Requirements should address the avoidance of: • Rescue ICSI • Use of spermatids - In addition, requirements should include: • Genetic testing of males/couples depending on the diagnosis • Genetic counseling (discussed in a separate document)
Improper performance of ICSI	- Procedure performed by a qualified person - Requirements should address: • the selection and immobilization of a viable spermatozoon • the correct positioning of the oocyte prior to injection - Gametes and *in vitro* embryos should be handled in a manner which protects their quality - The handling of gametes and *in vitro* embryos should be performed using sterile technique
Use of inappropriate equipment and materials	- If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity

	- Appropriate equipment for the purpose intended, the volume and the type of procedures performed - The equipment should be clean and disinfected
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
	- Have suitable procedures in place to double-check the identification of gametes and *in vitro* embryos
Improper Records	- Records should be kept indicating each and every occasion when gametes and *in vitro* embryos are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of gametes and *in vitro* embryos, such as serial numbers/batch numbers of equipment and materials coming into direct contact with gametes and *in vitro* embryos or data related to monitoring and maintaining the required conditions
	Records should also include: - patients identification - infertility diagnosis - the origin of sperm used (e.g., ejaculated, epididymal, testicular) - type of spermatozoon used - the number of oocytes injected - the number of oocytes fertilized - the number of ICSI *in vitro* embryos transferred and cryopreserved - date and time of the ICSI procedure - whether any problems occurred during the procedure (adverse events)

In vitro embryo Culture and Assessment

Contributing Factors	Proposed Control Measures
Improper *in vitro* embryo culture and assessment	- Procedure performed by a qualified person - Written procedures for *in vitro* embryo culture and assessment should be in place - Requirements should address the following criteria: • the presence of two pronuclei • the time window for the assessment of fertilization • the separation of normally fertilized oocytes - In addition, requirements should include: • criteria regarding oocytes showing delayed fertilization • criteria for *in vitro* embryo scoring/grading - *In vitro* embryos should be handled in a manner which protects their quality - The handling of *in vitro* embryos should be performed using sterile technique
Use of inappropriate equipment and materials	- If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity
	- Appropriate equipment for the purpose intended, the volume and the type of procedures performed - The equipment should be clean and disinfected
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)
	- Have suitable procedures in place to double-check the identification of gametes and *in vitro* embryos
Improper Records	- Records should be kept indicating each and every occasion when

	gametes and *in vitro* embryos are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of gametes and *in vitro* embryos, such as serial numbers/batch numbers of equipment and materials coming into direct contact with gametes and *in vitro* embryos or data related to monitoring and maintaining the required conditions
	Records should also include: - Patients identification - The relative time for fertilization - The stage of *in vitro* embryo development prior to *in vitro* embryo transfer - The quality or grade of each *in vitro* embryo - Whether any problems occurred during the procedure (adverse events)

In vitro embryo Transfer

Contributing Factors	Proposed Control Measures
Improper *in vitro* embryo transfer	- Procedure performed by a qualified person - Written procedures for *in vitro* embryo transfer should be in place - Requirements should address the following criteria: • the type of catheter used • the use of ultrasound guidance • the number of *in vitro* embryos to be transferred (e.g., number transferred relative to the age of the woman) • the method of transfer • the stage of *in vitro* embryo development at transfer - In addition, requirements should include: • catheter flushing after *in vitro* embryo transfer - *In vitro* embryos should be handled in a manner which protects their quality - The handling of *in vitro* embryos should be performed using sterile technique
Use of inappropriate equipment and materials	- If media or protein supplements are purchased, there should be documentation of quality control testing supplied by the manufacturer
	- If prepared in-house, established documented procedures should include a documented method for quality control of the media and all media supplements
	- The quality of the contact material (i.e. culture dishes, pipettes, etc.) should be tested and documented
	- Use appropriate methods to maintain temperature, pH and osmolarity (especially in instances where the embryology laboratory and the transfer room are not in close proximity)
	- Use of appropriate equipment for the purpose intended
Misidentification	- Proper labeling of the container (such as name and date of birth and using indelible ink)

	- Have suitable procedures in place to double-check the identification of gametes and *in vitro* embryos
Improper Records	- Records should be kept indicating each and every occasion when gametes and *in vitro* embryos are handled, and by whom
	- Records should encompass any data that may enable traceability of factors having an impact on the quality and safety of *in vitro* embryos, such as serial numbers/batch numbers of equipment and materials coming into direct contact with gametes and *in vitro* embryos or data related to monitoring and maintaining the required conditions
	Records should also include: - Patients identification - The stage of *in vitro* embryo development at *in vitro* embryo transfer - The number of *in vitro* embryos transferred and justification - The type of catheter used - The method of transfer - Whether any problems occurred during the procedure (adverse events)

Appendix C

List of Documents Analyzed on AHR

Our policy analysis involves research and analysis of various standards from national and international accreditation bodies, professional guidelines and codes of practice. The following standards/guidelines/codes of practice were examined:

- The Canadian Council on Health Services Accreditation (CCHSA) Assisted Reproductive Technology (ART) Laboratory Services, 2006.
- The Guidelines for the Number of Embryos to Transfer Following *In Vitro* Fertilization by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Canadian Fertility and Andrology Society (CFAS), 2006.
- The Association of Clinical Embryologists (ACE) Accreditation Standards and Guidelines for IVF Laboratories.
- The International Organization for Standardization (ISO) Medical Laboratories – Particular requirements for quality and competence 15189, 2003.
- The College of American Pathologists (CAP) Commission on Laboratory Accreditation, Reproductive Laboratory Checklist, 2005.
- The Fertility Society of Australia Reproductive Technology Accreditation Committee (RTAC) Code of Practice for Centres Using Assisted Reproductive Technology, 2002.
- The European Society of Human Reproduction and Embryology (ESHRE) guidelines for good clinical practice in IVF laboratories, 2000.
- The Practice Committee of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) revised guidelines for human embryology and andrology laboratories, 2004.
- The Human Fertilisation and Embryology Authority Code of Practice 6th ed. 2003
- The National Collaborating Centre for Women's and Children's Health Clinical Guideline by the UK National Institute for Clinical Excellence (NICE). February, 2004.
- Minimum standards for ICSI use, screening, patient information and follow-up in WA fertility clinics. Western Australia, January 2006.
- World Health Organization. Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 4th Edition. Cambridge University Press, 2000.
- World Health Organization. WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge University Press, 2000.