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Arja Halkoaho

Ethical Aspects of Human Tissue Research

Views of the Stakeholders

Publications of the University of Eastern Finland
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UNIVERSITY OF
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ARJA HALKOAHO

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ABSTRACT

Ethics is a central aspect in scientific research. Most of the studies on ethics have focused on informed consent from the point of view of the participants. There are few studies on the views of different stakeholders in research using human tissues. However, this kind of data, if available, could contribute to research ethics by both improving the ethical conduct of recruitment and may increase participation.

The aim of this study was to describe the ethical aspects of tissue research and to learn how the stakeholders in research involving human tissues perceive their participation and how the protection of their rights is guaranteed by the ethical framework.

The study consisted of four stages. Studies 1-2 included interviews with mothers (n=25) who donated their placenta for placental perfusion studies and with midwives (n=20) who were involved in recruiting mothers for the placental perfusion studies. Study 3 participants were researchers (n=23) who were participated in perfusions studies of human placenta, representing nine different nationalities. The data in study 3 were collected from the researchers by focus group interviews (n=12) and an open-ended questionnaire (n=19, eight also attended a group session). In study 4, the data consisted of scientists' ethical statements (n=56) which were collected from all the applications (n=688) received by the official regional ethics committee in the Hospital District of Northern Savo during 2004-2009. The data were analyzed by using thematic content analysis.

The stakeholders in placental perfusion studies considered the perfusion study as important, and in particular the mothers and midwives supported the use of placentas for such purposes. This study revealed the challenges encountered in clinical research concerning successful recruitment and the informed consent process in order that potential participants can give informed consent for research. Societal meaning of tissue research is multidimensional and consists of the significance of scientific knowledge, the public image of science and aspects of research ethics. Active communication was regarded as crucial and should include both the public and the scientific community.

In conclusion, tissue research was seen as important since it benefits society as whole. If research projects are be conducted in an ethically acceptable manner, then they must based on a functional organizational structure and cooperation with research group. The significance of ethical topics in the use of human tissue for research purposes will still further increase in the future. Therefore, continuing awareness and education about research ethics is essential.

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TIIVISTELMÄ

Etiikka on keskeinen osa tieteellistä tutkimusta. Etiikan alalla tutkimukset ovat kohdentuneet pääasiassa tietoon perustuvan suostumuksen toteutumiseen tutkittavien näkökulmasta. Eri viiteryhmien näkemyksiä tutkimusetiikasta on julkaistu niukasti. Tältä alueelta tutkimustiedon tuottaminen voi edistää eettisten näkökohtien huomioon ottamista rekrytoinnissa ja siten lisätä osallistumista tutkimukseen. Tämän tutkimuskokonaisuuden tarkoituksena on kuvata kudostutkimuksen eettisiä näkökohtia sekä eri viiteryhmien osallisuutta ja oikeuksien toteutumista eettisestä näkökulmasta tieteellisessä kudostutkimuksessa.

Tutkimuskokonaisuus koostuu neljästä osatutkimuksesta. Näistä kahden ensimmäisen empiirisinä aineistoina olivat äitien (n=25) ja kätilöiden (n=20) haastattelut. Äidit luovuttivat istukan perfuusiotutkimukseen ja kätilöt osallistuivat äitien rekrytointiin. Kolmas osatutkimus kohdentui istukkaperfuusion tutkijoihin, jotka edustivat yhdeksää eri kansallisuutta. Aineisto kerättiin ryhmähaastattelun (n=12) ja avoimia kysymyksiä sisältäneellä kyselylomakkeella (n=19, näistä kahdeksan tutkijaa osallistui myös ryhmähaastatteluun) avulla. Neljäs osatutkimus koostui vastaavien tutkijoiden eettisistä lausunnoista (n=56), jotka kerättiin Pohjois-Savon sairaanhoitopiirin tutkimuseettiselle toimikunnalle toimitetuista lausuntohakemuksista (n=688) vuosilta 2004–2009. Aineistot analysoitiin temaattisen sisällön analyysillä.

Viiteryhmät pitivät istukkaperfuusiotutkimusta tärkeänä. Erityisesti äitien sekä kätilöiden mielestä istukan käyttäminen tällaiseen tutkimukseen on merkittävää. Tämä tutkimus osoitti rekrytoinnin onnistumisen ja tietoon perustuvan suostumuksen kannalta tärkeitä haasteita kliinisessä tutkimuksessa. Suostumuksen hankkimisprosessi on suunniteltava huolellisesti, jotta tutkimukseen osallistuva pystyy antamaan tietoon perustuvan suostumuksensa. Kudostutkimuksen yhteiskunnallinen merkitys on moniulotteinen. Keskeisiä elementtejä siinä ovat tieteellisen tiedon painoarvo (merkittävyys), tieteen profiili ja tutkimusetiikka. Aktiivista kommunikaatiota sekä eri viiteryhmien välillä että kansalaisten, poliittisten päättäjien ja tieteellisen yhteisön välillä, pidettiin välttämättömänä.

Kudostutkimus on tärkeää, eteenkin, jos se hyödyttää koko yhteiskuntaa. Kliinisen tutkimuksen onnistuminen eettisesti hyväksyttävällä tavalla edellyttää myös organisaation hallinnossa toimijoiden ja tutkimusryhmän välistä yhteistyötä. Eettisten näkökohtien merkitys kudostutkimuksessa kasvaa tulevaisuudessa, jonka vuoksi tutkimusetiikan koulutus on tarpeen.

Yleinen Suomalainen asiasanasto: etiikka, tutkimusetiikka, bioetiikka, istukka, tietoon perustuva suostumus, sisällönanalyysi, kvalitatiivinen tutkimus

To Tuomas and Johannes

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Finally I want to save the kindest and warmest words to the people who are dearest to me. My loving thoughts are always with my parents who have passed away. My sister Anne and her family have been a great support for me and also practical help with the transcription of the tapes. Also my sister Leila and my brother Reijo and their families deserve my deepest thanks. With you, around the table in "Lammin takana" my heart and mind are peaceful.

My words are not enough to express my love to my husband Tapio and sons Tuomas and Johannes. You all have faith in me and support in difficult times. I thank you for being in my life.

Kuopio April 2012

Arja Halkoaho

List of the original publications

This dissertation is based on the following original publications:

I Halkoaho A., Pietilä A-M., Dumez B., Van Damme K., Heinonen S., Vähäkangas K. 2010. Ethical aspects of human Placental Perfusion: interview of the mothers donating placenta. Placenta 31, 686–690.

II Halkoaho A., Vähäkangas K., Häggman-Laitila A., Pietilä A-M. 2012. Views of midwives about ethical aspects**:** participation in Placental Perfusion Studies. Midwifery 28, 131-137.

III Halkoaho A., Pietilä A-M., Vähäkangas K. 2011. Ethical Aspects in Placental Perfusion Studies: Views of the researchers. Placenta 32, 511–515.

IV Halkoaho A., Pietilä A-M., Vesalainen M., Vähäkangas K. 2011. Ethical aspects in tissue research - Thematic analysis of ethical statements to the research ethics committee. Re-submitted.

Contents

Abbreviations

IRB	Institutional Review Board
CIOMS	Council for International Organizations of Medical Sciences
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
CDBI	Steering Committee of Bioethics
HBM	Human biological material
ICM	International Confederation of Midwives
ICMJE	The International Committee of Medical Journal Editors
NIH	U.S. National Institutes of Health
REC	Research Ethics Committee
UNESCO	United Nations Educational, Scientific and Cultural Organization
TUKIJA	National Committee on Medical Research Ethics
VALVIRA	National Supervisory Authority for Welfare and Health
WHO	World Health Organization
WMA	World Medical Association

1 Introduction

Ethics is a core component of all in scientific research. It is a generic term for various ways of understanding and examining moral life (Beauchamp & Childress 2001). The ethics of medicine have developed from the time of Hippocrates to the present day (Beauchamp & Childress 2001), in fact experiments on human beings may be as old as medicine itself (Leder 2009). Socially marginal and physically vulnerable individuals, like slaves and prisoners, were often subjects for human experimentation. Experiments performed by Nazi doctors are recognized as being the most heinous medical crimes against humanity in the twentieth century (Leder 2009). These historical incidents of questionable practices in human biomedical research created the need for international regulations e.g. the Nuremberg Code in 1947 and later the Declaration of Helsinki (1964-2008), which detail the ethical principles for medical research involving human subjects and it is a binding declaration for physicians. In the past decades, a number of regulations about medical research have been issued both at the international and national levels (WMA, World Medical Association, 2011). The Declaration of Helsinki defines that pre-evaluation of the research plan should be performed by an independent research ethics committee (Beauchamp & Childress 2001, Halila 2007, WMA 2011). The Declaration of Helsinki had an influence on the establishment of ethics committees worldwide and this triggered a shift towards focusing on the moral obligation of obtaining the informed consent of research subjects (Beauchamp & Childress 2001, Vähäkangas 2004, Halila 2007, Ebbesen 2009, 2011). In Finland, according to the current legislation, five health care districts have official research ethics committees that evaluate all biomedical studies on humans and human tissues from an ethical and legal perspective (Keränen et al. 2011).

The Declaration of Helsinki has been incorporated into the laws and/or legislations of many countries, including Finland, and international conventions such as the convention on Biomedicine of the Council of Europe, the CIOMS Guidelines on Biomedical Research and the UNESCO Declaration on Biomedicine (Halila 2007). As a consequence of the development of medical science and related biomedical ethics, the discipline of bioethics was also established. Much of the research conducted within the academic philosophical disciplines of bioethics has focussed on theoretical reflections on the adequacy of ethical theories and principles (Pellegrino 1999, Ebbesen 2009, 2011). Nevertheless, ethical dilemmas resulting from rapid medical progress mean that one must to view bioethics as a social movement. Increasingly, bioethics is moving towards multidisciplinary collaboration (Pellegrino 1999). The most commonly used principles are the so- called four principles of biomedical ethics: autonomy, justice, beneficence and non-maleficence (Beauchamp & Childress 2001). However, alternative principles have been introduced (Rendtorff 2002, Ebbesen 2009, Lev 2011, Vähäkangas 2011) and lately there has been a shift towards a more global perspective (Ijsselmuiden et al. 2010, Vähäkangas 2011) and solidarity (Lev 2011, Vähäkangas 2011). Two major points have arisen, those also find support in the literature, first biomedical principles should be employed to promote discussion (Häyry 2003) and secondly they should be used in everyday work in biomedical practice (Ebbesen & Pedersen 2007, 2008). Overall, discussions in research ethics need to continue (Lipworth et al. 2008, Vähäkangas 2008, Anderson & Sieber 2009). Incidents of questionable practices in human biomedical research have also occurred in recent history (e.g. see White 2005, Caplan & Moreno 2011).

Science is a developing and ongoing process and ethics should be of the forefront of this development (Vähäkangas 2004) and there is a need for humanization of medical education and practice for healthcare personnel (Pellegrino 1999). In Finland, a government bill called the Act of Biobank has been introduced to Parliament in October 2011, and if Parliament

agrees, the Act will come into force in 2013. Nevertheless, there has been little discussion about tissues used in research in Finland (Tupasela 2004, Vähäkangas & Länsimies 2004) although public opinion is considered as being important (Tupasela 2004, Vähäkangas & Länsimies 2004, Tupasela et al. 2007).

There is very little research into the special ethics of performing studies involving pregnant women. Most studies have focused on clinical trials in pregnant women where potential physical harm to both the mother and baby has been the main objective (McCullough et al. 2005, Helmreich et al. 2007, Wild 2007). However, while other types of research not directly related to medical adverse-effects or harm are still meagre, pregnant women have been considered as a vulnerable group. Midwives and nurses have an important role in recruiting mothers for scientific research (Hicks 1995a, Hicks 1995b, McSherry 1997). During recruitment, it is important to appreciate how best to distribute facts about the studies so that the mothers and families can make informed decisions and acceptance of the responsibility for the outcomes of their choices (Beauchamp & Childress 2001, ICM International Confederation of Midwives 2012). It is noteworthy that research examining the involvement of midwives in scientific biomedical research is scarce and the publications that are available mainly investigate the situation existing in the 1990s (Hicks 1995a, Hicks 1995b, Mc Sherry 1997, Meah et al. 1996). These studies indicated that the midwives expressed feelings of lacking sufficient knowledge or the skills to explain research as well as the confidence to judge their role in the research (Meah et al. 1996). Furthermore, ICM (2012) as well as World Medical Association (WMA 2011) state that scientific research should take into account national laws and international guidelines, such as the Declaration of Helsinki. There are only a few studies concerning researchers and ethical aspects in tissue research (Santa et al. 2007, Campbell et al. 2008). In comparison, there has been work done listing the opinions of scientists or medical doctors working in genetic research (Hallowell et al. 2009, Ruiz-Canela et al. 2009), clinical trials (Mason et al. 2000) and clinical settings (Ferguson 2003, Fisher-Jeffes et al. 2007, Hansson et al. 2007).

The ethical discussion in tissue research has focused mainly on informed consent (Vermeulen et al. 2009 ab, Treweek et al. 2009, Mancini et al. 2011) especially in biobank research (Vermeulen et al. 2009 ab, Petrini 2010a). In contrast, although human placenta has been used in research rather extensively (Prouillac & Lecoeur 2010) the ethical aspects of using placenta have been very rarely discussed (Vawter et al. 2002, Jenkins & Sugarman 2005, Salvaterra et al. 2006, Lind et al. 2007). One research model involving the placenta is placental perfusion (Schneider et al. 1972, Vähäkangas & Myllynen 2006). The aim of the human placental perfusion studies in our research group has been to study transplacental transfer and placental effects of food carcinogens as a part of an EU project, NewGeneris (Contract no. FOOD-CT-2005–0163202). This research program is international and multidisciplinary and its objectives are to promote fetal and child health by identifying factors in the environment which could be detrimental to the fetus. In these studies, the term placenta was collected after the birth from healthy women and the tissue, which remained anonymous, was perfused using a well-defined method (Schneider et al. 1972, Pienimäki et al. 1995, Annola et al. 2008, Annola et al. 2009) in a university laboratory.

The ultimate aim of this study was to examine the ethical aspects in tissue research from the point of view of different stakeholders. Ethics is an integral component of scientific research and it is important to appreciate how the stakeholders in the tissue research perceive their participation and the protection of their rights as guaranteed by the ethical framework.

2 *Review of the literature*

2.1 ETHICAL PRINCIPLES IN BIOMEDICAL ETHICS

2.1.1 Human dignity

Human dignity can be seen as a core concept in biomedical ethics, being indispensable in the moral discourse (Haugen 2010, Jordan 2010, Kotalik 2010). It refers to a collection of intangible, distinctively human attributes such as moral virtue, appreciation of beauty, awareness of oneself as a unique individual, participation in the human community, receptivity and personal agency such as courageous or compassionate (Jordan 2010). According to Kotalik (2010), the respect of human dignity is a concept consistent with deontologal, natural law, human rights and other ethical theories. Haugen (2010) also has considered dignity as a human rights principle and has insisted that public policy decisions need to ensure that they adhere to the goal of upholding human dignity. The value of dignity was recognized already in the year 1948 in the United Nations Universal Declaration of Human Rights. Article 1 states: *"All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood."* More recently, human dignity has been included up in international declarations, for example, the UNESCO (United Nations Educational, Scientific and Cultural Organization) International Declaration on Human Genetic Data and in the Declaration of Helsinki (Lötjönen 2002, Halila 2007, Haugen 2010). In the literature, dignity is also closely linked with integrity and vulnerability (Kottow 2004). Attention has also been given to the consideration that dignity is a complex concept because it can mean different things to people who are differently situated, for instance, it possesses cultural dimensions (De Melo-Martin 2011).

Macklin (2003a) has claimed that the concept of dignity is useless in medical ethics. Macklin (2003a), examined the documents of the international human rights instruments and conducted that "dignity" seems to have no meaning beyond what is implied by the principle of medical ethics, or respect for persons: the need to obtain voluntary, informed consent; the requirement to protect confidentiality; and the need to avoid discrimination and abusive practices. In turn, Killmister (2010) has criticized Macklin´s arguments by saying that the usefulness of dignity as a guiding principle in medical ethics can be much improved by identifying the single conceptual link that ties together the various values flying under its banner. This link is based on the concept that dignity is the capacity to live by one's standards and principles. In addition, dignity can play two roles: it is both a universal capacity that forms the foundations for the value of human life, thus making it an appropriate concept to be included in human rights and bioethics documents in general; and it serves to articulate which actions are required for that capacity to be met, in particular the absence of humiliation (Killmister 2010). In addition, Haugen (2010) has pointed out that dignity applies to everyone in the same way as autonomy or vulnerability, but the latter two concepts differ between individuals depending on their abilities, external conditions and specific situations.

The development of biomedical science has been rapid, also in research with human tissue, and many questions have been raised during this process e.g. about genetic information (Vähäkangas 2004, Vähäkangas 2008, Kirchhoffer & Dierickx 2011, Nuffield Council on Bioethics 2011). From an ethical point of view, genetic heritage and genetic data can be regarded as unique, and the general understanding is that it differs from other health information (see e.g. UNESCO 2012, Vähäkangas 2008). According to the literature, the relationship between human dignity and the use of human tissue does not provide any easy answers for biomedical research and practice. Nevertheless, it has been argued that

dignity is not a simple criterion and that it is possible to judge which types of treatment of human tissue can violate human dignity. Although the majority of research on human tissue may not violate human dignity, understanding the moral relevance of where the tissue comes from and to what end will it be used make the concept of human dignity useful (Kirchhoffer & Dierickx 2011).

2.1.2 Other ethical principles

Ethics is about leading a good life, about realizing our dignity and the dignity of others (Kirchhoffer & Dierickx 2011). Vähäkangas (2004) has argued that if one accepts that ethics can be understood as a reflection of existing moral principles, then the requirements for good ethics extend beyond laws and moral principles. In scientific research, this also means it is necessary that the scientists improve their personal involvement. Furthermore, if ethics are concerned with moral and personal values, it cannot be value-free, and the same concept also applies to research ethics. Ethics can be seen as a reflection of moral principles based on the historical perspective and aimed towards the future (Vähäkangas 2004). Most ethical theories and traditional medical codes presuppose that there are ethical principles and values. A set of principles in a moral code can be seen as an analytical framework that expresses the general values underlying rules of common morality. The best known principles of bioethics are 1) the respect of autonomy, 2) the principles of beneficence, 3) non-maleficence and 4) justice formulated by Beauchamp & Childress already in 1989 (see Beauchamp & Childress 2001).

The critics of these four principles have directed towards the principles themselves, their inapplicability in real life and their excessive individualism, i.e. their insistence that people are always more important than the values prevailing in their communities (Häyry 2003). Consequently, the literature has emphasized the difficulty of demonstrating the concept of morality in a concrete manner, as those four principles form a part of a common morality or a collection of very general norms (Herissone-Kelly 2011). The principles have also been difficult to apply to problems involving certain societal issues e.g. biobanking (Nilstung & Hermeren 2006). Rendtorff (2002) argued that ethical principles cannot be understood as universal everlasting ideas or transcendental truths but they rather function as reflective guidelines and important values in European culture. Rendtorff & Kemp with coworkers identified four European ethical principles: respect for autonomy, dignity, integrity and vulnerability. The justification for these principles was seen in the fact that they have been implemented in legislations throughout Europe, e.g. Constitution of Finland, and take better account of vulnerable individuals (Rendtorff 2002, Ebbesen & Pedersen 2007, 2008). In addition, the Belmont report (1979) prepared by the U.S. National Institutes of Health (NIH) identified the essential ethical principles as follows: respect for persons, beneficence and justice. The principle of respect for persons can thus be divided into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. In scientific research, this kind of respect for persons is ensured when adequate standards for informed consent are satisfied (NIH, 1979).

However, the rapid development of science has triggered criticism towards these basic principles (Ebbesen 2009) especially in human tissue research (Hansson 2010). Ebbesen (2009) pointed out that difference between different definitions of the principles stem from the views of the authors about human nature and their philosophical and cultural backgrounds. Furthermore, Launis (2001) raised the issue of whether coherentism can provide the best guidance for moral justification in modern biotechnology because there is a lack of objective moral values. In addition, moral principles play a dual role in bioethics not only serving as normative guidelines but also representing the source of moral theory (Launis 2001). It has also been argued in the literature that the existing principles might be too narrow (Ijsselmuiden et al. 2010) and restrict the advance of medical knowledge (Schaefer et al 2009, Hansson 2010). Ijsselmuiden & coworkers (2010) anticipated that in the future, research ethics will involve an intensification of the focus of the role of research in

achieving global justice. They devised three values based on their hopes about the future development of ethical consideration: solidarity, respect for Southern innovation and commitment of action. Hansson (2010) argued that a narrow view of autonomy could even harm the interest of patients. Furthermore, Schaefer and coworkers (2009) pointed out that participation in research is a critical way to support an important public good, and consequently, all individuals have a duty to participate.

The Nuffield Council on Bioethics (2011) considered what ethical values influenced research with human tissue. It is notable that they included, in addition to autonomy and justice, also altruism, dignity, maximizing health and welfare, reciprocity and solidarity as ethical values. According to Vähäkangas (2011) the principles can also be regarded from the point of view of either the individual or at the population/global level. The relevant principles on the individual level are beneficence and non-maleficence, justice, autonomy and confidentiality, whereas the population or global level principles are: equality, solidarity, benefit sharing, global justice, cultural pluralism and responsibility. Lev (2011) also stated that solidarity, equality, personal responsibility and autonomy were valuable principles which should not be jeopardized in the context of biomedicine.

Despite the fact that different opinions about ethical principles and their suitability for biomedical research have been introduced, there is some uniformity in these definitions. Autonomy, including informed consent, has been adopted as a central concept in biomedical ethics by many authors (e.g. Beauchamp & Childress 2001, Rendtorff 2002, Lev 2011). In addition, privacy as a concept is closely linked with integrity and autonomy (Ursin 2010) but also with confidentiality (CDBI, Steering Committee of Bioethics 2011, Vähäkangas 2011) and integrity (Beauchamp & Childress 2001). Again, in the literature, justice is seen as the basic principle ensuring fairness and equity, vulnerability as well as solidarity (Rawls 1971, NIH 1979, Beauchamp & Childress 2001, Ijsselmuiden et al. 2010, Rogers & Kelly 2011, Lev 2011). Beneficence and non-maleficence as principles have been important part of medical ethics since the Hippocrates Oath, *"Do no harm"*, and can be regarded as still applicable today (Beauchamp & Childress 2001, NIH 1979, Ebbesen 2009).

2.1.3 Autonomy, privacy and voluntariness

Autonomy, including informed consent, has been adopted as a central concept in biomedical ethics by many authors. Autonomy includes liberty, privacy, self-governance (Beauchamp & Childress 2001) is based on morality and human dignity and includes aspects of integrity and vulnerability (Jordan 2010). Respect for the autonomous choices of an individual is a common moral principle, which has also been discussed in medical ethics in clinical settings from the point of view of patients (Gonen 2002, Hunt & de Voogd 2007, Nyrhinen 2007, Falagas et al. 2009, Rahman et al. 2011, Will 2011a,b) doctors (Fisher-Jeffes et al. 2007, Will 2011a,b) and nurses (Lee et al. 2009). Respect for autonomy is seen as the norm i.e. one must of respect the decision-making capacities of autonomous persons (Beauchamp & Childress 2001). Alternatively, O´Neill (2002) states that, a physician´s primary obligation is to act the best interest of the patient e.g. in emergency situations (see e.g. Halila 2007).

Autonomous action is an action to which people consent as free and equal rational beings, and they are to be understood in this way. A well-ordered society affirms the autonomy of persons and encourages them in making objective judgements of justice. (Rawls 1971). The concepts of autonomy and informed consent are also enshrined in the most important international guidelines (e.g. Declaration of Helsinki, ICH- Good Clinical Practice, CIOMS) and national legislation (Constitution of Finland, Medical Research Act, Act of Medical Use of Human Organs and Tissues). According to Haugen (2010), autonomy can be understood to embrace non-discrimination, participation, empowerment, rule of law and accountability. In addition, autonomy can be viewed as being embedded in the concept of human dignity (Haugen 2010).

In research, the principle of autonomy can be assessed through the process of free and informed consent. Although medical practice is expected to confer a health benefit for the patient, the nature of research means there is uncertainty about whether the participants will actually benefit from research participation and these kinds of benefits are not the main purpose of the research. Participants must be provided with appropriate, accurate and understandable information about the research before asking them to choose whether or not they wish to participate. In the context of biomedical research, an individual should be provided with the necessary conditions to exercise his or her autonomy, and a person whose autonomy is diminished or impaired needs to be protected from harm and abuse (Beauchamp & Childress 2001, Vähäkangas 2004, Hunter 2006, WMA 2011).

Privacy is closely connected with autonomy as well as human dignity and respect for the individual (Eriksson & Helgesson 2005a, Heikkinen 2007, Ursin 2010, Tännsjö 2011). Additionally, the concept of privacy is complex and involves different perspectives and dimensions; there is no single universal definition of privacy (Leino-Kilpi et al. 2001, Ursin 2010). The dimensions of the concept of privacy have been described through the concepts of physical, psychological, social and informational privacy. Furthermore, earlier studies clearly highlighted the importance of the concept of privacy in hospital organisations and have considered also the problems of implementation. The most common problems have to do with noise, limited space and restrictions. In addition, informational privacy is often concerned with the confidentiality of patient information (Leino-Kilpi et al. 2001, Schmidt et al. 2009, Casteleyn et al. 2010, Ursin 2010) and especially in tissue research with respect to personal genetic information (Hull et al. 2008, Tännsjö 2011, Ursin 2010). Public confidence in the use of health research data is essential (Kapp 2006) and it is important to develop good research governance, this has been stated to be in the interests of all stakeholders in research (van Veen 2008, Schmidt et al. 2009). According to Jackson & Lim (2011) there is a need for education to improve knowledge and practice of confidential data handling. The ethical point of view, this aspect is bound to take on increasing importance in the future with the continuing growth of scientific research (see e.g. Leino-Kilpi et al. 2001, Jackson & Lim 2011, Tännsjö 2011).

Similarly, voluntariness is emphasized as a part of autonomy, meaning that free and informed consent also implies that participants must not be coerced or unduly influenced. Undue influence may be financial in nature or, for instance, an attempt to influence close relatives (Beauchamp & Childress 2001, Vähäkangas 2004, CDBI 2011, WMA 2011). Nevertheless, the focus should not lie solely on the disclosure of information or decision-making but also on the effective communication and commitment between the parties involved in the research (Manson & O´Neil 2007, Sutrop 2011). There has also been speculation about whether the protection of individuals has gone too far and whether the need to achieve of autonomy and privacy has become an obstacle to research. As early as 1997, Van Damme and co-workers (1997) postulated that a broader consent in the context of genetic screening and genetic monitoring should be considered. The current discussion is also shifting from individual rights towards the common good, and it has been claimed that the form of informed consent and autonomy should be reconsidered, especially in human tissue research (Siegel et. al 2009, Sutrop 2011).

2.1.4 Justice and solidarity

Questions of justice have usually been associated with social practices such as punishment, taxation and political representation. In the year 1971, John Rawls introduced two principles of justice. According to the first principle, each person is to have an equal right to the most extensive basic liberties compatible with a similar liberty for others, and the second principle holds that, social and economic inequalities are to be arranged so that they are both (a) reasonably expected to be in everyone´s advantage and (b) attached to positions and offices open to all. Positive discrimination can be acceptable if it confers the greatest benefit to those worse off (Rawls 1971). Justice has been generally defined in relation to

biomedicine, but it also has relevance for research. The principle of justice can be considered as fairness and equity. One crucial question is who ought to receive the benefits of research and who should bear its risk and burden. In biomedical research involving human beings, this implies that the distribution of risk and burden on the one hand and benefit on the other has to be fair a principle known as distributive justice. Distributive justice carries with it implications especially for the selection of research participants: the selection criteria should be related to the purpose of the research (NIH 1979, Beauchamp & Childress 2001, CDBI 2011).

Justice cannot be viewed only as the protection of participants in health research but also as the broadening of peoples thinking in the social context of individuals´ lives by considering the complex influence of social differences and power relationships within the research process. Health research can be seen as an activity that promotes social justice (Rogers & Kelly 2011). In addition, it has been proposed that the ethics review should be expanded to consider wider health and socio-economical benefits, including intellectual property rights, technology transfer, institutional capacity strengthening as well as finding other ways of sharing the benefits of research (Ijsselmuiden et al. 2010). The focus should be on responsible research with considerations of the needs of the developing countries (Ijesselmuiden & Jacobs 2005, Ijsselmuiden et al. 2008, London & Kimmelman 2008, Matlin et al. 2008, Sewankambo & Ijsselmuiden 2008) and patients with limited language skills (Bhutta 2004, Casteleyn et al. 2010, Glickman et al. 2011) as well as tissue exportation from the developing countries to the developed world (Upshur et al. 2007, Andanda 2008, Zhang et al. 2010).

The selection of research subjects needs to be scrutinized in order to determine whether some groups (e.g. welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected because of their ready availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied (NIH 1979). One could consider the opposite case, whether a certain group is being systematically ignored, because of the difficulties to obtain informed consent or other reasons (Glickman et al. 2011, Iltis 2011). Rawls (1971) considered solidarity to have a special role in defining the principle of justice. Solidarity is described as a mutual attachment that people have towards each other, giving rise to various obligations such as the obligation to help people meet their basic needs. In addition, solidarity has also been described by using the following concepts: integration, commitment to the common good, empathy and trust (Lev 2011). In genomic research, for example, where no immediate clinical benefit is to be expected and where the key question is really whether we can be obliged to undertake sacrifices to benefit future patients, justice and solidarity can be regarded as the guiding principles (Hoedemaekers et al. 2007).

Subsidiarity as a principle has been introduced in the literature and this is connected closely to justice (Kotalik 2010). It has been found as suitable in the context of biomedical ethics (Pennings et al. 2004, Kotalik 2010). Subsidiarity means that matters ought to be handled by the smallest, lowest or least centralized competent authority. This is the only principle that addresses the issue of the locus of decision making, and it is strongly linked to human dignity, democracy and solidarity. Subsidiarity can be understood as a procedural manifestation of relational solidarity. It also supports and enhances human dignity by respecting the creativity of humans and because it holds a high regard for the freedom of individuals, families, groups and communities. It has been argued that the value of the Principle of Subsidiarity is that it can address the question of how and by whom decisions should be made in the context of biomedical ethics (Kotalik 2010).

2.1.5 Beneficence and non-maleficence – balance of benefits and harm

For a long time the Hippocratic maxim "do no harm" has been the central principle for medical ethics (NIH 1979, Beauchamp & Childress 2001). The Hippocratic Oath and its successors state that physicians have a fundamental medical duty to pursue the patient´s best medical interest, to avoid harm and to maintain the patient´s confidence (BMA 2004). The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. Research guidelines emphasize that the welfare of the research participant must be a primary concern. According to the legislations and international guidelines, it is unacceptable to prioritize the expected benefits to society over the welfare of individual people (BMA 2004, Medical Research Act, WMA 2011).

The principles of beneficence and non-maleficence together create a moral obligation to maximize potential benefit and minimize potential harm. The principle of beneficence also has further implications, in particular that the design of the research studies is sound and meets the accepted criteria of scientific quality. This also implies that the researchers are competent to carry out the research (Beauchamp & Childress 2001, CDBI 2011). All research projects need to undergo a thorough risk/benefit assessment; risk identification, estimation and evaluation are all stages in risk assessment. The participants' overall benefits from the research project must clearly be higher than the potential risks (Beauchamp & Childress 2001).

In clinical research, participants should understand the distinctions between usual care and research. The absence of this knowledge has been termed as the therapeutic misconception (Lidz et al. 2004, Miller & Joffe 2006, Appelbaum & Lidz 2006). Pelias (2004) pointed out that in tissue research, and especially research in human genetics, the researcher should consider the tensions between doing no harm to the participant and the participant's personal autonomy. These tensions arise from the question of whether the participants will have the right to see their own results, the accuracy of which may not be guaranteed. Eriksson & Helgesson (2005b) have also brought up the concept of moral harm in the use of tissue samples for future use. For example, moral harm could be created when samples would be used for research to which participants would strongly object.

2.2 REGULATIONS CONCERNING TISSUE RESEARCH IN FINLAND

2.2.1 Application of international guidelines nationally

In biomedical research, human tissues are a valuable resource, but their use also carry ethical (Vähäkangas 2004, Cambell et al. 2008) and legal considerations (Campbell et al. 2008, VanVeen 2008). Many international regulations have been drafted based on national legislations. In the Convention for the Protection of Human Rights and Fundamental Freedoms, ratified in Finland in May 1999 (63/1999) and the EU member states have agreed to support the Universal Declaration of Human Rights proclaimed by the General Assembly of the United Nations on the 10th of December 1948. These international declarations of human rights and ethical principles form the basis for national and international regulations.

In addition to national legislation, there are several international guidelines and recommendations (table 1) that have important roles in advancing international discussion, interpreting and amending legal instruments and serving as grounds for judicial decisions when legislation is not comprehensive (Lötjönen 2004). The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration was first adopted in 1964 and it has been amended eight times since that date, most recently in 2008 when research on identifiable human material and data was included in the declaration. The declaration provides guidelines for recruitment, the informed consent process as well as for balancing the risks and benefits.

Confidentiality and aspects concerned with the scientists' skills and the ethics review are also included. The declaration states that the physician must make an effort to gain consent for collecting, researching, storing and reusing samples. If consent from the tissue donor is difficult to obtain or this difficulty threatens the quality of the research, then the ethical committee can also grant permission for the research without the donor's consent (WMA 2011), which is in contravention of Finnish legislation, e.g. Finnish Act of Medical Use of Human Organs and Tissues (see table 2). In addition to the Declaration of Helsinki, some well-known examples include the CIOMS (Council for International Organization of Medical Sciences) and ICH-GCP (International Conference on Harmonisation - Good Clinical Practice) guidelines, the latter of which was used as a reference when preparing the European Union Clinical Trials Directive (Lötjönen 2004).

CIOMS (Council for International Organization of Medical Sciences) in collaboration with WHO (World Health Organization) has published the International Ethical Guidelines for Epidemiological Studies (2008) concerning research with stored biological samples and related subjects for future epidemiological research. According to Guideline 24, an investigator in this field must obtain the voluntary informed consent of the individual donor. If the individual is not capable of giving an informed consent, the permission should be obtained from the legally authorized representative of the donor in accordance with applicable law. The research proposal must also be submitted to an ethical review committee. If the stored samples had been collected for a past research, clinical or other purposes without informed consent, the ethical review committee may consider waiving the consent if it proves materially unfeasible to obtain consent. The 2009 amendment of CIOMS concerning informed consent states that, with certain conditions, the ethics committee may consider whether new consent is needed for work involving the use of old samples (CIOMS 2011).

Both the Declaration of Helsinki and CIOMS emphasize the importance of voluntary informed consent. However, these guidelines also pay particular attention to tissue research and the difficulties in obtaining consent. A special status is given to the ethics committee and the review process. This has been taken into account in the Finnish Government bill on biobanks, where much attention has been paid to the review process in accordance with both guidelines.

Table 1. Some useful sites on medical bioethics including human tissue research

Organization	Content includes	Internet address
World Medical Association, WMA	Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subject	www.wma.net
Council for International Organizational of medical sciences, CIOMS	International Ethical Guidelines for Biomedical Research Involving Human Subjects	www.cioms.ch.
UNESCO	International Declaration on Human Genetic Data	www.unesco.org
Council of Europe, Steering Committee on Bioethics (CDBI)	Purpose is to protect human rights and dignity in the field of biomedical research. Its purpose is to define and safeguard fundamental rights in biomedical research, in particular of those participating in research.	http://www.coe.int/t/dg3/healthbioethic/cdbi/INF_2011_%201%20E%20info%20doc%20cdbi.pdf
Nuffield Council on Bioethics	An ethical and legal framework for the use human tissue	http://www.nuffieldbioethics.org
Nordic Committee on Bioethics	Identify and survey ethical issues related to legislation, research and developments in biotechnology in the Nordic countries and internationally.	www.norden.org

2.2.2 Ethical aspects in legislation in Finland

In Finland, the basis for the rights and liberties of people are established in the Constitution of Finland (731/1999). The Constitution is also an important Act concerning medical ethics and its principles (Lötjönen 2004). According to the Constitution of Finland, everyone is equal before the law and no one shall, without an acceptable reason, be treated differently from other persons on the ground of sex, age, origin, language, religion, conviction, opinion, health, disability or other reason that concerns his or her person. The Act also contains aspects about children, stating that children shall be treated equally and as individuals, and they shall be allowed to influence on matters pertaining to them to a degree corresponding to their level of development (Constitution of Finland).

Research utilizing human tissues is firmly regulated by Finnish national legislation: Medical Research Act (488/1999, 295/2004, 794/2010) and Act of Medical Use of Human Organs and Tissues (101/2001, 547/2007, 778/2009, 653/2010) as well as Personal Data Act. Privacy and handling confidentiality of personal information are also included in the Act on the Status and Rights of Patients (785/1992) and The Act on The Openness of Government Activities (621/1999) (see table 2 more detailed content.).

The most important Act concerning medical research in Finland is the Medical Research Act, which states that research conducted under this act shall respect the inviolability of human dignity. The Medical Research Act came into force in 1999 with amendments appearing in 2004 (295/2004) and 2010 (729/2010). The Act defines medical research as research involving intervention in the integrity of a person, human embryo or human foetus for the purpose of increasing knowledge of health, the causes, symptoms, diagnosis,

treatment and prevention of diseases or the nature of diseases in general. In 2010, an amendment (729/2010) extended the coverage of this Act to cover other areas of health research which may violate human integrity (Medical research Act, Halkoaho et al. 2010, Keränen et al. 2011). The Medical Research Act also regulates how the ethical pre-evaluation is to be done by independent ethics committees. In addition, the risks and benefits of the research must be considered carefully. Furthermore, the Medical Research Act emphasizes the participants' personal autonomy and informed consent and considers the position of vulnerable groups. According to the law, medical research cannot be conducted without the research subject's informed consent. The Medical Research Act does not define human tissue research in detail.

The Act of the Medical Use of Human Organs and Tissues (101/2001, 547/2007, 778/2009, 653/2010) regulates the medical use of human organs, tissues and cells, as well as how to consider the change to which the tissue samples are being put in medicine and medical research. The Act describes different possibilities to use tissue in research and is concerned with entire consent procedures i.e. from obtaining informed consent from the subject up to authority permission. According to this Act, human tissues and cells are defined as follows: all tissues and cells taken from humans for a specific research use, including haematopoietic stem cells from peripheral blood circulation, umbilical cord and bone marrow, gametes, fetal tissues and cells, as well as adult and embryonic stem cells. This law has been amended three times since its enactment when the European Union Commission Directives 2004/23/EC, 2006/17/EC, 2006/86/EC concerning e.g. standards of quality and safety for donation human tissues and cells (not concerned with research, e.g. in vitro research or animal models, using human tissues and cells) were included in the act (Act of the Medical Use of Human Organs and Tissues).

The objectives of the Personal Data Act (523/1999) are to implement, the aspects of privacy and handling confidentiality in scientific research. It also highlights the details of personal data which are: 1) any information on a private individual or the members of his/her family or household, and 2) their personal characteristics or personal circumstances, where these are identifiable as concerning this data (The Personal Data Act). A human sample does not fulfill the definition of personal data, because a sample itself does not contain information related to the person. However, when linked to information related to the person, a sample can become a part of his/her personal data. If the sample cannot be identified as belonging to a certain individual, the Personal Data Act cannot be applied. Nonetheless, confidentiality and privacy will play a major role in the forthcoming Finnish Biobank Act (HE 86/2011).

A national regulation (117/2010) has also enforced a convention for the protection of Human Rights and the dignity of the human being with regard to the application of biology and medicine: The Convention on Human Rights and Biomedicine. The parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. The interests and welfare of the human being shall prevail over the sole interest of society or science. An intervention in the health field may only be carried out after the person concerned has provided free and informed consent to be a part of this research. This person shall beforehand be given appropriate information about the purpose and nature of the intervention as well as its consequences and risks. The person concerned may freely withdraw his or her consent at any time (Convention on Human Rights and Biomedicine 2011). These laws address several ethical aspects concerning human tissue research: the ethical review process, avoiding harm, confidentiality of personal information, and the informed consent process. Nevertheless, it is also apparent that some societal aspects are missing such as how to consider tissues being stored in a biobank research as well as a population and global perspective.

Table 2. Relevant legislation and content concerning tissue research in Finland (www.finlex.fi)

Regulations	Main content	Ethical aspects
Constitution of Finland	Everyone has the right to life, personal liberty, integrity and security. The right to privacy, which also includes one's right to freely control oneself and one's body.	Human dignity, integrity, privacy, equality
Medical Research Act (488/1999, /2004,/2010)	Regulate Medical Research: ➢ The scope, definition and general conditions governing medical research ➢ People in charge of research ➢ Regional and national ethics committees ➢ Weighing up benefits and harmful effects ➢ Informed consent (form, from and whom), possibility to withdrawn consent ➢ Research involving persons not able to consent, minors, pregnant women and nursing mothers, prisoners or forensic patients ➢ Define clinical trials on medicinal products, good clinical research practice ➢ Define research involving embryos and fetuses	Ethics committee review process, avoiding harm, informed consent process, vulnerability
Finnish Act of Medical Use of Human Organs and Tissues (101/2001, 547/2007, 778/2009, 653/2010)	Regulate as follows the use of tissue sample when change in purpose for which tissue samples will be used: ➢ Taken for therapeutic or diagnostic purposes: the patient's consent or his/her legal representative's permission. National Supervisory Authority for Welfare and Health (Valvira) can give permission for the surrender or use of tissue samples taken for therapeutic or diagnostic purposes or to establish the cause of death in situations in which the person's consent is impossible to obtain. ➢ Taken for medical research purposes may be surrendered and used for medical research other than that stated in the consent document only with the consent of the person concerned. If the said person has died, Valvira can give permission for such research if justifiable cause exists. ➢ Taken for therapeutic or diagnostic purposes, or to establish the cause of death may be surrendered and used for medical research and teaching purposes with permission from the health care unit or other unit for whose activities the sample was taken without personal data.	Informed consent, privacy
Personal Data Act (523/1999)	Regulate the processing of personal data, the protection of private life and the other basic rights which safeguard the right to privacy, to promote the development of and compliance with good processing practice. Personal data may be processed for purposes of historical or scientific research for a reason.	Privacy and handling confidentiality of personal information.
The Act on the Status and Rights of Patients (785/1992)	Everyone living permanently in Finland, without discrimination, have the right to health care and medical treatment. The treatment must be organized in a way that does not violate the person's human dignity and respects his/her personal conviction and privacy. Defines also the basic principles of preserving samples and models taken during therapy.	Human dignity, privacy, confidentiality
The Act on the Openness of Government Activities (621/1999)	Regulates on the right to obtain information from public documents of the authorities and on the authorities' professional discretion. A sample of human origin does not constitute a document defined in the act; however, a sample may be part of the document when the sample or information about the sample is attached to the document describing or defining the sample.	Confidentiality and privacy
Act of Biopank Goverment bill 89/2011 (under consideration by the parliament)	Will include the following topics: ➢ Ethical review process ➢ Structure of the biobank ➢ Management issues ➢ Consent (form, from whom) ➢ Information about the use of tissue sample, source of information and check-up possibility ➢ Withdrawal	Informed consent process, confidentiality and privacy

2.2.3 Ethics committee review process

In most countries, the majority projects in health research, including tissue research, involving human participants is reviewed by a Research Ethics Committee (REC). Within the European Union, this is legally mandatory for all clinical trials with medicinal products for human use. In addition, many countries require similar levels of review for all medical research (Lötjönen 2004, Hedgecoe et al. 2006, Klitzman 2011). In addition, there may be some practical reason for the review process e.g. requirements of medical journals (ICMJE 2012).

Internationally, there has been discussion about the number of ethics committees (Wainwright & Saunders 2004, Klizman 2011) and whether all medical studies need to be reviewed e.g. non-invasive studies (see e.g. Hearnshaw 2004). This has also been an agenda in Finland (Halila 2009). In 2009 Halila (2009) highlighted the fact that the current situation might benefit from reducing the number of research ethics committees, since this could lead to more experienced members and higher-quality reviewers. In Finland, the Medical Research Act amendment in 2010 actually reduced the number of ethics committees (Halila 2009, Keränen et al. 2011) and focused on the competence of the members (Keränen et al. 2011).

Research ethics committees are constituted and function in various different ways. In some countries, the ethics committees may be linked to public health or research institutions as well as to hospitals. In addition, most countries have local and central or national committees (Wainwright & Saunders 2004, Hedgecoe et al. 2006, Moerman et al. 2007, Halila 2009, EU 2011, Klitzman 2011). However, there are several principles that have to be followed to ensure that the committees are competent to perform the task assigned to them. The most important principle is independence in order to avoid conflicts of interest. In addition, ethical and scientific expertise is needed to be able to review protocols, as well as a degree of diversity among the members chosen to represent the general public. (EU 2010). Ethics committees weigh ethical aspects against national regulations (Casteleyn et al. 2010, Holm 2011) and against ethical principles. Criticism has been expressed that the ethics committees are too bureaucratic (Spence 2011) or too strict (Hansson 2010) or the process takes too long (Keinonen et al. 2003). In addition to the above criticisms, Casteleyn and coworkers (2010) have listed some aspects that have been brought up in the literature such as organizational aspects, lack of diversity in opinions that are represented and professional competence of the members of ethics committees (Casteleyn et al. 2010). Furthermore, some critics have highlighted the question of gender equality among committee members (Dickenson 2006, Moerman et al 2007).

Nevertheless, Edwards and co-workers (2004) pointed out that differences between the judgments of ethics committees may not be problematic. They also insisted that consistency of the ethics committee as a regulatory or governance process will never achieve perfection. Holm (2011) has argued that self-regulation by scientists themselves is not sufficient to achieve an ethically acceptable balance of the different interests that may be at stake. He recognized that strict conformity to ethical rules may not be desirable, but there seems to be no better alternative than the current system of ethics review boards (Holm 2011). Good communication between the scientists and the ethics committee is critical in order to guarantee a thorough handling of all ethical aspects of research and in this way to ensure protection of research participants and the scientists i.e. preventing mishandling of their study and patients (Vähäkangas 2004, Ylitalo 2006, Taylor et al. 2008, Merlo et al. 2007). It is arguable that despite the criticism that has been leveled against the ethics committee review process, independent ethics committees also have their advocates in the literature.

2.2.4 Avoiding harm and confidentiality of personal information

One of the most important ethical aspects in biomedical research is avoiding harm. It is generally accepted in laws and guidelines that research subjects may be exposed only to measures where the expected health or scientific benefits are unequivocally greater than the potential risks or harm to the research subject (The Medical Research Act, WMA 2011). Avoiding harm and risk has been highlighted in the literature which has been concerned with the legislation (Miller & Joffe 2009, Rid et al. 2010) although but not overlooking the possibility of overprotection of the participants (Miller & Joffe 2009). However, Van Ness (2001) criticized use of the concept of risk in biomedical research. His perception was that risk infers the possibility of harm. The concept of harm is clearly unintended and undesirable in biomedical research projects. Therefore, when using the concept of risk, ethical vigilance is required e.g. thoughtful planning of clinical trials taking into account both ethical aspects and methodological considerations (Van Ness 2001).

In medical ethics, a boundary has been drawn between clinical research and clinical medicine and the putative research participant should understand the difference between research and care, the so-called therapeutic misconception (Lidz et al. 2004, Miller & Joffe 2006, Appelbaum & Lidz 2006). For instance, research participants may sign the consent to participate in a clinical research with only a modest appreciation of the risk or the disadvantages of participation (Appelbaum & Lidz 2006). However, it has been questioned whether integration between care and research can provide better care and would thus be ethically achievable (Beauchamp 2011, Hansson & Chadwick 2011, Largent et al. 2011). Even though it is accepted that integration may provide better care to the patients, the general opinion is that research participants should be aware of the difference between care and research and that this kind of information must be provided in a comprehensible manner.

Using left-over samples of from diagnostic and therapeutic procedures and their subsequent use in research is common in clinical settings. However, it is necessary to discuss whether this kind of research causes harm to the participants and whether any informed consent is needed (Kapp 2006). However, the question of whether the sample should be large enough for both clinical care and research has been rarely discussed. This raises an ethical question, especially in research with children (see e.g. Reid 1994). The Act of the Medical Use of Human Organs and Tissues (101/2001) states that, using samples in research must not hamper the use for, which they were originally intended. Moreover, the risk of harm caused by tissue research has also been connected with genetic research, from the point of view of privacy and confidentiality (Goodson & Vernon 2004) and the invasiveness of the procedures (Gillet 2007, Vähäkangas 2008).

In the Belmont report, vulnerability was linked to the selection of subjects. Macklin (2003b) describes vulnerability as referring to instances when an individual or groups are subject to exploitation. In addition, regulations and policy documents provide some focus on the limitations of an individual´s capacity to provide informed consent (Levine et al 2004). Vulnerability is also seen as one of the ethical principles by Rendtorff & Kemp (Rendtorff 2002), and in the literature, being at the core of human rights (Haugen 2010). Particular attention is paid in the literature to the most vulnerable groups e.g. children (Iltis 2009, Haugen 2010). However, according to the literature, it is not always clear who is vulnerable, even though vulnerability has been a prominent aspect in the research ethics literature and the regulations concerning human research (Coleman 2009). Vulnerability typically has been understood in terms of the ability to give or withhold informed consent and the likelihood of being mislead, mistreated or otherwise taken advantage of in the research. A criticism has been expressed for designating as vulnerable groups, those who are seriously ill (cancer patients), terminally ill patients and minors (Hurst 2008, Iltis 2009). Iltis (2009) pointed out that some authors have argued that the categories of people now being considered as vulnerable are so diverse that virtually all potential human subjects could be included. Lev (2011) pointed out that when children are considered as a

vulnerable group, biomedical progress might be problematic. This question can arise with new innovations, especially in genetic research when parents consent on behalf of their children.

Confidentiality can be regarded a special case of privacy protection in tissue research as well as other biomedical research. It is evident that anyone who has access to someone's personal information has a duty not to pass on that information to outsiders or to use it for ends other than those agreed upon. In this sense, confidentiality could be viewed as making it an ethical and legal duty of the individual or group which has gained access to the information to keep it confidential (see e.g. Ursin 2010). In tissue research, confidentiality has been viewed as a high priority among ethical aspects because of the possibility to access genetic information (see e.g. Vähäkangas 2008). In confidentiality, the key ethical and legal issue is not only whether study participants are adequately and equally protected but whether, at the same time, scientific progress is being safeguarded (Casteleyn et al. 2010). In tissue research, confidentiality also depends on whether samples are identifiable, coded, encrypted or anonymous (Goodson & Vernon 2004, Kapp 2006, Vähäkangas 2008, Schmidt et al. 2009). In the literature, the terminology about labeling samples varies and sometimes causes confusion (Vähäkangas 2004, Vähäkangas 2008). Patients may be anxious to know whether their samples will be used for further purposes either identifiably or anonymously (Hull et al. 2008, Tupasela et al. 2010) and whether their consent also includes providing access to their personal clinical data (Mancini et al. 2011). Moreover, public opinions may differ on whether sponsorship involves domestic or international sources (Hemminki et al. 2009). The discussions about harm and confidentiality have stressed the importance of continuing the research and discussion of ethical aspects in tissue research.

2.2.5 Informed consent process

Informed consent to research derives from a legal doctrine and it comprises three elements: *Relevant information* is provided to a person who is *competent to make a decision* and who is acting *voluntarily* (Beauchamp & Childress 2001, Vähäkangas 2004, Appelbaum et al. 2009, WMA 2011). Beauchamp & Childress (2001) have introduced elements of informed consent: 1) Threshold elements are competence and voluntariness. 2) Information elements are material information, recommendation of a plan and understanding. 3) Consent elements are decision and authorization of the chosen plan. Similarly, according to the Belmont, report there is a widespread agreement that the consent process can be considered as containing three elements: information, comprehension and voluntariness (NIH 1979). Hence, the participation in any study requires that the participants are fully competent to give consent for their participation. The consent must be a voluntary choice, and as a basis of this choice, the participants to have information presented to them in a manner they can comprehend. After this, the putative participant can make his or her own choice to participate and thus authorise the research staff to act according to the plan (Beauchamp & Childress 2001, Vähäkangas 2004).

There are many studies about informed consent in research e.g. in neonatal research (Mason et al. 2000), healthy voluntary participants (Kass et al. 2007, Länsimies-Antikainen et al. 2007, 2010a,b), emergency research (Halila 2007, Parvizi et al. 2008) and clinical settings (Wendler & Grady 2008). According to the literature, major future challenges include the consent for future biobank storage and unforeseen future research (Hansson et al. 2006, Hofmann 2009, Secko et al. 2009, Toccaceli et al. 2009) and interpretations of the concept of autonomy and informed consent in different cultures (Bhutta 2004, Casteleyn et al. 2010). The Medical Research Act states that information about research must be given so that research subjects are in a position to provide informed consent. This has been recognized in the literature: the importance and challenging nature of the timing of the consent has been stated as important (Vähäkangas 2004, Cahana & Hurst 2008, Hewitt et al. 2009) and the different kinds of procedures to obtain genuine informed consent have been claimed to require a rethinking (Hamilton et al. 2007, Cahana & Hurst 2008, Schwartz &

Appelbaum 2008, Hofmann 2009, Hewitt et al. 2009, Wendler 2011). It is known also that understanding of research information is limited in research participants (Crepeau et al. 2011, Desch et al. 2011, Monson et al. 2012) and different types of presentations of information are needed (Monson et al. 2012).

Cases of potentially impaired voluntariness have also been raised as an issue in numerous contexts: compensation for entering a research study, recruiter being the subject´s own physician, drug abuse of participants, patient's lack of other access to medical care and coercion by some person in a position of authority, e.g. husband or tribal leader. However, according to the literature, the presence of influence does not mean that the decision is not voluntary. The decision becomes involuntary if it is subject to a particular type of influence that is external, intentional, illegitimate and causally linked to the choice of the subject (Appelbaum et al. 2009).

Informed consent may have a different meaning in different types of human tissue research. For instance, it has been discussed whether the use of archived pathology samples or human tissue samples given anonymously requires any specific informed consent (Kass et al. 2007, Bathe & McGuire 2009). Vermeulen & coworkes (2009a, b) in their studies have aimed to determine the procedure by which patients can influence the use of their samples for research purposes. The majority of the patients preferred the "opt-out plus consent" procedure where individuals are actively informed (verbally and by means of a leaflet) about the possibility to opt-out of all future research being done with their tissues. Particularly in biobank and epidemiological research, a broad type of consent has been raised as one possibility (Aromaa et al. 2003, Hansson et al. 2007, Stjernschantz Forsberg et al. 2009, 2010, 2011). The prerequisite for broad consent is that there is public education and debate on issues such as the necessity of research, the risks involved, and the safeguards that society has put in place to protect both individuals and groups of people against harm (Vähäkangas 2004, Hansson et al. 2007, Stjernschantz Forsberg et al. 2009, 2010, 2011). In comparison, Nuffield Council on Bioethics (2011) recommended that when a patient consents to medical treatment involving the removal of tissue, that consent should be taken to include consent to subsequent disposal, storage or acceptable use of the tissue, provided that such use has been regulated by appropriate ethical, legal and professional standards. Genuine consent needs to be based on adequate understanding of the treatment, and explanations used in the consent procedures must make it clear that consent will include acceptable further uses of tissue removed during treatment. When comparing recommendation of the Nuffield Council and the existing literature from recent years, their most apparent difference concerns the form of consent. Most scientists would recommend a broader consent than proposed by the Nuffield Council. Again, latest report of Nuffield Council recommended that it is acceptable to ask participants to agree to their sample being used in any future research that is within the broad aims of the biobank and has been approved by a research ethics committee (Prainsack & Buyx 2011).

It is also stated in Finnish law, the Medical Research Act (488/1999, 295/2004, 794/2010), that the research subject can withdraw his or her consent at any point prior to the completion of the research. This right must be informed before the start of the research. Withdrawal of consent and the resulting withdrawal from the research cannot cause any negative consequences for the research subject (Medical Research Act). In the international literature, there has been some discussion about whether withdrawal from research is acceptable in all situations (Chwang 2008, McConnell 2010). Chwang (2008) argued that in some cases, researchers must have a guarantee that subjects will not withdraw, and they must waive the right to withdraw from the study in order to produce beneficial results. However, McConnell (2010) came to the conclusion that any waiver of the right to withdraw would be unnecessary and if it were implemented, its overall impact would likely be negative.

2.2.6 Societal aspects

In Finland, legislation on the biobank of government bill has been introduced to the Parliament in October 2011, and if Parliament agrees, the Act will enter into force in 2013 as the Biobank Act (Table 2). The role of the ethics committee is becoming central in the reviewing process (Watson et al. 2010) and informed consent process will be one of the key issues incorporated into the new Biobank law (Kääriäinen 2011).

Biobank research has been widely discussed internationally (Eriksson & Helgesson 2005b, Bell et al. 2009, Coebergh et al. 2006, Hansson et al. 2006, Nilstun & Hermeren 2006, Melas et al. 2010, Stjernschantz Forsberg et al. 2009, 2010, Watson et al. 2010). Tupasela and co-workers (2010) conducted a population survey (n=2400) into attitudes of Finns aged 24-65 about the use of existing diagnostic and research samples, the setting up of a national biobank and different types of informed consent. The response rate of the study was 50%. Most of the respondents (83%) had little or no knowledge of what biobanks were and 77% regarded biobanks in a positive manners. About one in every three would not attach any conditions to their consent, almost half (41%) considered it important to regain consent when a new study contained several steps. There were respondents (30%) who wished to consent to be gathered for every new research project and would like to decide in which type of research their samples would be used (44%). One third of both men and women were willing to allow the use of their samples in research involving private enterprises. Furthermore potential participants wished to receive more knowledge about tissue donation (Tupasela et al. 2010).

Internationally there has been some discussion about the ethics of using samples from deceased subjects in the context of longitudinal biobanking genetic research stressing the importance of using these samples in research (Tassé 2011). In Finland, in such situations the National Supervisory Authority for Welfare and Health, Valvira, can give permission to use these samples for research (The Act of the Medical Use of Human Organs and Tissues). New Biobank law will legislate on this matter (HE 86/2011).

There seems to be consensus across professionals who work with human tissue, for a reform of the law towards a communitarian approach (Campbell et al. 2008) and to gather broad consent from participants (Stjernschantz Forsberg et al. 2009, Kääriäinen 2011). Consent is regarded as important, but tissues have been seen as a valuable resource for the entire community. One implication of this would be that the current emphasis on individual choice could be detrimental to the overall interests of society. (Tupasela 2008, Campbell et al. 2008). Clearly, one can envisage cases when there would be tension between individual rights and common good (Campbell et al. 2008).

2.3 APPLICATION OF ETHICAL PRINCIPLES IN TISSUE RESEARCH

2.3.1 Types of tissues used for research and their implications

The use of human biological materials and associated personal data are increasingly important for biomedical research (Vähäkangas 2008, CDBI 2011). The Nuffield Council on Bioethics (2011) has launched a general list of the types human tissue samples used in tissue research: 1) Organs and parts of organs 2) Cells and tissue 3) Sub-cellular structures and cell products 4) Blood 5) Gametes (sperm and ova) and 6) Embryos and fetal tissue. In clinical settings, human tissue for research purposes is removed from the body during the course of diagnosis or treatment, but may not be needed for these purposes anymore. Procedures that may furnish excess tissues can be surgical, diagnostic, clinical research, transplantation and/or autopsy: eg. amniotic fluid or pieces of chorion villus (part of the placenta) may be taken for cytogenetic or other diagnostic tests during pregnancy. Small pieces of tissue may be taken by biopsy for pathological examination and diagnosis, and larger amounts of tissue may be removed surgically during an operation for malignant or other diseases (Bell et. al. 2009, Allen et al. 2010, Nuffield Council on Bioethics 2011). In Finland, placenta is considered as waste and it is an example of a human tissue with a specialized function during the pregnancy in the body. However, once the placenta has completed its function and has been expelled from the body after birth, it is usually abandoned by mothers and is generally regarded as clinical waste. Occasionally, the placenta may be used to extract proteins of therapeutic value, such as albumin, which can be used for treating burns (Nuffield Council on Bioethics 2011). (Table 3.)

The Steering Committee of Bioethics (CDBI 2011) categorized the materials that are taken from human beings for research use as falling into two broad categories: those that are destined for immediate use in a specific research project, and those that are to be stored for future use. According to the CDBI, this distinction is not absolute, in that part of a sample may be used straight away and the remainder retained for subsequent use. Furthermore, the CDBI states that the ethical issues for research involving human biological materials are two-fold: issues concerning initial removal of the material, which necessitates a physical intervention, and issues of consent/authorization and confidentiality concerning use and/or storage of the materials that have been removed.

Table 3. Source and use of human tissue for research and ethical aspects

Source	Examples	Ethical aspects	References
Diagnostic or therapeutic procedures	Blood or serum Scrapes of surface cells Many organs or tissues	Invasiveness of the procedures Personal information, Storage, Genetic data, biobank Difference between care and research Informed consent Risks/benefits	Vähäkangas 2004 Kapp 2006 Gillett 2007 Hamilton et al. 2007 Cambell et al. 2008 Hewitt et al. 2008 Al-Qadire et al. 2010
Autopsy specimens	Many organs and tissues	Storage, Consent biobank	Kapp 2006 Gillett 2007 Cambell et al. 2008 Tassé 2011
Tissue from healthy volunteers	Small skin biopsies (for example fatty tissue) Blood Buccal cells Hair root sample	Risks/benefits Informed consent, storage, genetic data, biobank	Merlo et al. 2007 Vähäkangas 2004 Petrini 2010b Caplan & Moreno 2011
Body waste	Urine, faeces, sweat, hair, nail clippings	Informed consent process	Kapp 2006
Waste tissue	Placenta, cord blood	Informed consent Genetic data Storage, Biobank	Vawter et al. 2002 Lind et al. 2007 Petrini 2010a

2.3.2 Ethics in human tissue research

Regarding ethical aspects in tissue research, several topics have been addressed in the literature. The aim of the literature search was to determine what methods have been used related to the ethics in research with tissue specimens and have a general overview about this topic. The search was done with an information specialist in order to identify the most appropriate search terms. Search terms, databases and process of data selection are presented in appendix I. A total of 19 studies were selected as providing examples about studies in tissue research in clinical settings. The biobank research was excluded and thus some difficulties were encountered. The reason for this was that researchers appeared to collect samples for future use which may be called a biobank. If consent had been sought during care in the clinic and the purpose was to store samples for future use, then those articles were accepted into this survey (e.g. Mancini et al. 2011, Morrell et al. 2011).

This literature consisted of qualitative (n=4), quantitative (n=7) studies and reviews of empirical studies (n=8) (Tables 4, 5, 6). The issues investigated and discussed in the literature commonly are *informed consent* (Faber et al. 1995, Furness & Nicholson 2004, Pentz et al. 2006, Campbell et al. 2008, Vermeulen et al. 2009 a,b, Treweek et al. 2009, Hens & Dierickx 2010, Mancini et al. 2011), *attitudes towards tissue research* (Farber et al. 1992, Cambell et al. 2008, Treweek et al. 2009, Hens & Dierickx 2010, Furnesss & Nicholson 2004, Morrell et al. 2011), *willingness to donate tissue* (Furnesss & Nicholson 2004, Pentz et al. 2006, Morrell et al. 2011), *IRB and consent* (Merz et al. 1999). Discussion in the reviews of empirical studies have focused mostly on *informed consent* (Hoeyer & Lynöe 2006, Santa et al. 2008, Porteri & Borry 2008, Petrini 2010a, *regulation and research governance* in tissue research (Meslin & Quaid 2004, Hakimian & Korn 2004, van Veen 2008, Steinman 2009).

2.3.3 Qualitative tissue research

Studies with qualitative methods (Table 4) mostly focused on informed consent of the study participants (Hens & Dierickx 2010, Mancini et al 2010, Morrell et al. 2011) but also views of professionals about ethical aspects in tissue research (Campbell et al. 2008). Hens & Dierickx (2010) interviewed adults and children, focusing on informed consent and different types of tissue donation, and on confidentiality. According to the results gained in the focus-interviews, it was found to be meaningful with respect to what kinds of tissue samples were being sought for research. The interviewed participants did not perceive a high risk associated with research on stored tissue, however they believed that confidentiality must be ensured. On the other hand, Mancini and co-workers (2011), used two different methods, interviews and questionnaire, in their study to determine opinions about informed consent in tissue research and use samples for future use. The opt-in consent (each person is informed about the research and their consent is sought) was the most popular option of the different forms of consent, but patients had difficulties in remembering or understanding what they had consented to. For example, patients did not know that they also consented to providing access to their personal clinical data later in the context of the biobank. Therefore Mancini and co-workers (2011) suggested that the informed consent process needed improving, which was in agreement with the conclusions of Hens and Dierickx (2010). Morrell and co-workers (2011) pointed out that even though the time available for decision was short; no sense of compulsion and manipulation was noticed.

Tissue research in general was seen as beneficial and risk-free (Hens & Dierickx 2010, Morrell et al. 2011) except for the involvement of private companies and access to data (Morrell et al. 2011) unless they were in the area of medical practice (Hens & Dierickx 2010). However, no reward was expected by the participants (Morrell et al 2011) and research was seen as good for the community (Campbell et al. 2008, Morrell et al. 2011) and a more communitarian approach was suggested (Campbell et al. 2008). Some concerns about confidentiality were also brought up (Hens & Dierickx 2010, Mancini et al. 2011) and therefore anonoymous samples were considered as safe (Hens & Dierickx 2010). Opinions between adults and teenagers differed with respect to privacy protection. Teenagers showed great confidence towards scientists and were curious about research findings (Hens & Dierickx 2010).

Campbell and co-workers (2008) stated that more education was required about ethical aspects in tissue research aimed at the professionals. In addition, it was stated that debate on ethical aspects in tissue research was needed. It was evident that the law itself was not sufficient and many ethical issues extended to areas beyond those covered by legislation. Three main areas of ethical concerns were identified by the writers: 1)the balancing of individual rights and social benefit to the community; 2)the efficacy of the new procedures for consent; 3) and the helpfulness for professional practice of the new legislation and regulation. They concluded that recognition of these concerns could help in generating a new partnership between professionals and patients and their families (Campbell et al. 2008).

Table 4. Examples of methods used in qualitative studies concerning ethics in tissue research.

Authors, year	Method	Focus
Campbell et al. 2008	Interview study	Professionals (n=31) who had specific insights into different aspects of work with human tissue and organs.
Hens & Dierickx 2010	Focus-group interview study	Attitudes towards research on human stored tissue samples may be dependent on the cultural context. 10 groups with 76 participants adults and children.
Mancini et al 2011	In-depth interviews and questionnaire	Opinions of cancer patients about consent process to donate tumor samples to research. Interviews n=19. Questionnaire n=745. Response rate 77%.
Morrell et al. 2011	In-depth interview	Attitudes of different stakeholders (n=12) towards tissue donation. Stakeholders were: patients (n=4), parents of children (n=2), health advocates (n=3), consumer representatives (n=2), indigenous representative (n=1).

2.3.4 Quantitative tissue studies

There were seven studies which were selected as examples of quantitative tissue studies (Table 5) Four of the studies focused on clinical care with left-over tissue (Vermeulen et al. 2009a,b, Pentz et al 2006, Furness & Nicholson 2004). One study investigated public opinions about leftover blood sample for future use (Treweek et al. 2009). The opinions of medical students (Farber et al.1992) and researchers (Merz et al. 1999) were also investigated.

Attitudes towards donating tissues for research were positive (Pentz et al. 2006, Treweek et al. 2009, Vermeulen et al. 2009b) but not without consideration about the ethical aspects (Vermeulen et al. 2009 a,b, Treweek et al. 2009). Informed consent was one of the main points raised (Farber et al. 1992, Vermeulen et al. 2009 a,b Treweek et al. 2009). Even though people were willing to give consent to research and future use of samples (Furness & Nicholson 2004, Pentz et al. 2006), they were anxious to know about the possible use of their samples. Otherwise, most patients feel that if they have been adequately informed then there is no need to be asked for more than one-time general consent (individual is informed and actively asked for written permission for all future studies) for research with residual tissue. Nonetheless, some patients regard residual tissue as a part of them and few consider residual tissue to be waste (Vermeulen et al. 2009 a,b). In a comparison of different consent procedures, Vermeulen and co-workers (2009b) pointed out that the so- called opt-out plus procedure (individuals are actively informed, verbally and by means of a leaflet, about the possibility to opt-out of all future research with their tissues) which they considered the best consent form, may unify two moral principles: patients are being informed but medical research can progress without unnecessary hindrance. Nonetheless, an open-ended consent was also considered as suitable for research with stored blood samples. Furthermore, linkage of samples to medical records was considered acceptable as long as the research had been approved by a research ethics committee (Treweek et al. 2009). Furness & Nicholson (2004) stated that misuse of tissue samples can impact on the general public´s opinions in the United Kingdom (UK) and strict regulations have led to abandonment of international studies in UK.

The literature also indicates that there is a need to educate researchers about the requirements involved when conducting tissue research such as the use of identifiable tissues as well as requirements for an Independent Review Board (IRB) review. Thus, some human tissue research was performed without IRB approval. Investigators who did not

obtain IRB approval did not understand the requirements (Merz et al. 1999). Faber and co-workers (1992) suggested that researchers should spend more time discussing with patients in clinical settings and inform patients and obtain consent for the research. It was also noticed by the authors that the third and fourth year students were less adamant about the need to inform patients than first and second year students. Those who had experience with tissue research were more comfortable with requesting tissues from patients than those who had not participated in this work (Faber et al. 1992).

Pentz et al (2006) found that it was essential to take care of cultural aspects and to ensure that the language used was understandable. However, no differences were found between two different ethnic groups in their opinions about the donation of biological samples for research. Most of the patients, regardless of the site of care, ethnicity or socioeconomic status, were willing to provide a biological sample for research which would be conducted without contacting the patients again. However, the authors stated that time given for consideration about consent was important (Pentz et al. 2006).

Table 5. Examples of methods used in quantitative studies concerning ethics in tissue research.

Authors, year	Methods	Focus
Vermeulen et al. 2009a	Questionnaire	To determine which consent procedure patients would prefer for future research with tissue stored following surgery. Patients (N=103), who had recently undergone surgery for breast or colorectal cancer
Vermeulen et al. 2009 b	Questionnaire and telephone interviews, comparative study	To determine what kind of consent procedure patients prefer and what are the effects of consent procedures on actual consenting behaviour. Options were: One time consent procedure n=60 (response rate 93%), Opt-out plus n=77 (response rate 93%), Control group, standard procedure, opt-out n=131 (response rate 88%) and telephone interviews (n=31, n=37, n=62).
Treweek et al. 2009	Questionnaire, survey	Attitudes of people recruited through general practices to donation and storage of blood left over from routine clinical tests in general practice (N=2471), response rate 34%.
Pentz et al. 2006	Questionnaire, comparative study	To compare the views of two groups of patients who were given the option of tissue banking. African American and white American cancer patients (N= 453), response rate 70%.
Furness & Nicholson 2004	Questionnaire	To obtain general consent for research use of surplus tissues from renal transplant biopsies in the renal transplant unit in Leicester.
Merz et al. 1999	Review of Journals and telephone survey with questionnaire	To examine the degree to which published studies involving human tissue document IRB approval and informed consent. Original articles, research reports and technical correspondence of 9 journals (n=105 papers). Authors (n=85) in telephone survey with questionnaire.
Farber et al. 1992	Questionnaire	Attitudes of medical students (N=4057), towards informed consent and the patient-physician relationship in regard to the research use of tissue. Response rate 33.7%.

2.3.5 Theoretical aspects of tissue research

In the published literature, theoretical considerations about human tissue research with ethical aspects have been widely discussed (Table 6) Most of the reviews or considerations have involved the informed consent process (Hoeyer & Lynöe 2006, Santa et al. 2008, Porteri & Borry 2008, Steinman 2009, Petrini 2010a). There is almost a consensus about the necessity of respecting the donors' personal choice (Santa et al. 2008, Steinman 2009, Petrini 2010), but problems arise from the ownership of the samples (Petrini 2010a) and the extent of information to be given to the participants (Porteri & Borry 2008, Meslin & Quaid 2004). However, as also supported by the literature, consent needs to be given without pressure (Hoeyer & Lynöe 2006, Porteri & Borry 2008, Steinman 2009, Petrini 2010a) and it should be clear who owns the samples (Petrini 2010a). In addition, the importance of tissue research is recognized (Meslin & Quaid 2004, Hakimian & Korn 2004, Santa et al. 2007, Steinmann 2009).

The informed consent process in the context of umbilical cord blood may be problematic for several reasons. For example, ownership of the sample has ethical and legal aspects. The question has been asked about whether the mother has the right to give consent or should the father also be involved. The general opinion is that the mother has right to sign the consent although involvement of the father may be recommendable (Petrini 2010a).

In the context of tissue banking, Steinmann (2009) has presented the opinion that the focus of autonomy should shift from individual capacity to autonomy as part of institutional practices and rules. The reason is that if the benefits of research are considered to lead to a common good and to satisfy interests of the general public, research has to be controlled through public intervention. Therefore, autonomy cannot be controlled by referring only to personal interest and individual self-determination (Steinmann 2009). Alternatively, Porteri & Porry (2008) stated that aspects of the donor need to be considered, she/he should be provided with individual sufficient information about the present and future use of samples. Also consideration of the specific biological and genetic aims of the research should be performed.

Santa and co-workers (2007) stated that ethical aspects in tissue research are important but for instance in retrospective studies with human tissue, it may be possible to guarantee donors rights by presumed consent. In addition, they considered that the benefits would likely outweigh any risk of damage to personal privacy or the very limited damage to property rights of an individual as long as personal choice had been respected. Likewise Hakimian & Korn (2004) stressed the importance of tissue research and its beneficence to the society which according to them can justify the fact that society can make exhaustive use of samples based on principle of justice.

Research governance of the tissue samples is seen requiring a fair balance between different stakeholders in research. Patients should be considered as biosocial citizens who are co-workers with researchers against the paternalistic attitudes of some ethicists and regulators (van Veen 2008). The basic principles of governance have been argued as requiring transparency (van Veen 2008) but not creating extra bureaucracy (van Veen 2008, Petrini 2010a) as well as protecting individual rights (Steinmann 2009). That is, research governance framework should not establish rules but principles which provide enough flexibility for the specifics of a project (van Veen 2008). In addition, education of the public and other stakeholders is needed (Meslin & Quaid 2004) not forgetting the responsibilities of the institutions (Hoeyer & Lynöe 2006, Steinman 2009). According to Meslin and Quaid (2004) regulatory reform will take some time, institutions and their ethics committees should begin to act to familiarize themselves with the projects involving HBMs (human biological materials) and begin to develop educational and policy strategies for anticipating difficulties in informed consent, assessment of risks and benefit and related human subject issues. Efforts should be made both to inform the public of the need for HBMs and to develop the policies and protections that would foster trust in such an endeavour.

Hoeyer & Lynöe (2006) concluded that ethical scrutiny should redirected away from informed consent towards issues concerning institutional arrangements and social responsibility.

Table 6. Examples about theoretical articles concerning ethics in tissue research.

Authors, year	Focus	Main results
Petrini C 2010a	Ethical issues of umbilical cord blood collection, storage and use.	Concept of informed consent is problematic because of the ownership of the cord blood. Content of the consent needs to be clarified as well as form of consent. Father's involvement is recommended for the consent process.
Steinman 2009	Concerns of the uncertainty in current proposition for the regulation of tissue donation.	If the benefits of research are considered to lead to a common good and to satisfy public interests, then research has to be controlled through public institutions. Autonomy does not exclude institutional support, as institutional support is the only way to take the autonomy of donors seriously.
Porteri & Borry 2008	Model of informed consent for the collection and storage of biological materials for research purposes.	Informed consent for the use of biological materials shall give donors sufficient information to make informed decisions about possible present and future use of the sample. Also consideration of the specific biological and genetic aims of the research should be performed.
van Veen 2008	Discussion about obstacles to European research projects with data and tissue.	Good research governance is a fair balance between the interests of all stakeholders. It should make the basic principles transparent on which observational research projects are based in line with European solidarity-based healthcare systems. Research governance framework should not establish rules but principles which provide enough flexibility for the specificity of a project.
Santa et al 2007	Use of human tissue in medical research and ethical considerations on it.	The benefits deriving from the use of human tissue are likely to be greater than any improbable risk of damage to personal privacy or very limited damage to property rights of the individual, as long if personal choice has been respected.
Hoeyer & Lynöe 2006	To explore the contribution from social anthropology to the medical ethical debates about the use of informed consent in research with human tissue.	There is reason to redirect the ethical scrutiny from informed consent to issues concerning intuitional arrangements and social responsibility. The authors suggest that an anthropologic approach could facilitate a reconsideration of the political implications of using informed consent as a regulatory practice in tissue-based research.
Hakimian & Korn 2004	Discussion about the legal, regulatory and ethical framework within human tissue research.	Human tissue specimens are unique and irreplaceable research source. Society's strong interest in the advancement of medical knowledge deserves a coherent and internally consistent legal, regulatory and ethical framework to govern specimen use. Society may justify the expansive use of these samples based on the principle of justice.
Meslin & Quaid 2004	Discussion about storage, use and regulation of human biological material (HBM) research, misuse of genetic information, economic factors as well as public knowledge.	Institutions and their IRBs should begin to act to familiarize themselves with the projects involving HBMs and begin to develop educational and policy strategies for anticipating difficulties in informed consent, assessment of risks and benefit and related human subject issues. Efforts should be made both to inform the public of the need for HBMs and to develop the policies and protections that would enhance trust.

2.3.6 Ethics in human placental research

The use of human placenta has increased in biomedical research in the past few years (Schneider et al 1972, Pienimäki et al. 1995, Vähäkangas & Myllynen 2006, Annola et al. 2009, Karttunen et al. 2010, Partanen et al. 2010). In an attempt to identify the published literature about ethics in human placental research, a systematic search was conducted in the PubMed, Ebsco and Scopus databases. The first search was done using terms placenta* ethics*, and 4 suitable articles could be retrieved (Appendix II) selected. Then a manual search was conducted in four journals: Bioethics, Journal of Medical Ethics, American Journal of Bioethics and Nursing but no relevant articles were found in this way. Two of the studies selected from the first search were about cord blood, which was not a keyword in this search. The reason for their inclusion was the consideration of recruitment process which can be used in placenta research generally as presented by Vawter et al (2006), and a discussion about ethical principles, informed consent and commercialization of research, as presented by Salvaterra et al (2006). Two of the selected articles were theoretical (Salvaterra et al. 2006, Vawter et al. 2006), one was a review (Jenkins & Sugarman 2005) and one article was based on qualitative interviews (Lind et al. 2007).

The ethical aspects of human placental perfusion were investigated in the study of Lind et al (2007). They interviewed 19 mothers and fathers in Denmark. The results showed that generally mothers were willing to donate the placenta for perfusion studies. They felt that face to face interaction, written information material and an informed consent form all played an important role in creating trust in this type of research. The mothers viewed the placental perfusion study as a gift to the health care system from the donor, and the importance of the medical research was the general opinion expressed. The interviews were performed one day before caesarean section (Lind et al. 2007).

The placenta and cord blood are known to be an important resource for stem cell research (Salvaterra et al. 2006). In a theoretical article Vawter and co-workers (2002) paid attention to the recruitment process in cord blood collection for research purposes. They argued that consent process could differ on whether consent was required or obtained before labour, during labour, or after collection for blood collected in utero or ex utero. One important factor was the participation of midwives or doctors in the decision-making capacity and if the mother was capable or interested, then brief information could be given. Consent should be asked after delivery. This is accordance with the work of Lind and co-workers (2007); their results indicated that some written information material should be provided to the participants in advance. However, some mothers mentioned that the mere opportunity for asking questions and making suggestions increased the degree of openness and created an atmosphere of trust.

Jenkins & Sugarman (2005) have highlighted the fact that incorporation of sensitivity to the cultural meanings and delineation of these meanings should be taken into account in all research involving human material. For instance, the placenta may have different significance in different nations e.g. companion to child, protection and healing, link of the child to the community and social identity of child, whereas in the Western world, the placenta is usually regarded as waste. The need of tissue for research materials has raised ethical questions e.g. how best to ensure continuing public support for the banking of human biological material and the protection of individuals and communities from harm as a consequence of participation in research (e.g. see Jenkins & Sugarman 2005).

On the other hand, Salvaterra et al (2006) pondered questions about ownership, informed consent and commercialization of cord blood banking, which they felt should also be taken into account. In their opinion, when cord blood was simply considered as a waste product of childbirth, its use did not raise ethical and legal questions with regard to ownership. However, at present, cord blood and the placenta itself have been identified as a valuable resource, and it has become crucial to identify owner rights for these materials.

Moreover, it is surprising, that there are so few studies concerning ethics in placental research in view of the fact that placenta has been used for decades as a valuable research

material for instance in studies investigating diseases of fetus with placental involvement (Guller et al. 2011), gene expression (Avila et al. 2010) and as a source of human proteins (Shin et al. 2010). It has been speculated that as the need for human models and tissue in research increases (Pasanen et al. 1990, Prouillac et al. 2010), important and new ethical aspects in research using tissue will emerge. From the ethical point of view, the opinions of different stakeholders will help in improving the practice of recruitment.

3 *Aims of the study*

Ethics is a fundamental aspect of scientific research. Most of the studies on ethics have focussed on informed consent from the point of view of the participants. There are few studies on the views of different stakeholders in research using human tissues. However, such data, if available, may contribute to improving the ethical conduct of recruitment and may increase participation in this kind of research.

This study is a part of a larger research programme on environmental carcinogenesis and fetal exposure to carcinogens. The placental perfusion method can be utilized to characterize fetal exposure to chemical compounds. The ultimate aim of this present study was to examine ethical aspects in tissue research. It is important to know how the stakeholders in research utilizing human tissues perceive their participation and how the protection of their rights is guaranteed by the ethical framework.

The specific objectives were as follows:

1. To evaluate the views of stakeholders i.e. placenta donors, recruiters and researchers, about the recruitment and informed consent processes in human placental perfusion studies.

2. To describe the views of stakeholders about the risks and benefits and confidentiality in human placental perfusion studies.

3. To assess the views of stakeholders in human placental perfusion studies about the societal meaning of scientific research.

4. To analyze how scientists consider the ethical aspects of their research.

4 Methods

4.1 PARTICIPANTS AND DATA COLLECTION

4.1.1 Participants in studies 1-3

Data were collected using multiple methods to interpret the stakeholders' views about the ethical aspects in tissue research. The purpose was to obtain an accurate representation of reality. Data triangulation was used to produce new and diverse information in the studied topic (Polit & Beck 2006).

Participants in studies 1-3 (original publications 1-3) were stakeholders in human placental perfusion studies: 1) mothers who donated their placenta 2) midwives who recruited the mothers and 3) human placental perfusion studies researchers. (Table 7.)

Study 1 participants were mothers (n=25) who gave birth at the University Hospital of Kuopio. They donated their placenta for the placental perfusion study and were asked one day after delivery for consent to be interviewed at a later stage. Participants met the following criteria: 1) able to give informed consent, 2) Finnish speaking and 3) living in the area of the Hospital District of Northern Savo. Recruitment for the first 4 interviews was carried out by the nursing staff at the ward. Four mothers were willing to participate in the interview and six refused. The first four participants recruited for the study suggested to the interviewer that she herself should be the one to carry out the recruitment for the interviews. Therefore, after the first four cases, the recruitment strategy was changed as proposed. The researcher became in charge of the recruitment herself and met 26 new mothers, of which 21 were willing to participate while only five mothers refused (thus the total number of interviewed mothers was 25). Mothers were given information about the interview both verbally and in a written form. If the mother was interested in participating, she gave her telephone number and she was contacted one week after discharge. Mothers were asked to discuss the study with their families and they were told about the possibility to withdraw their consent by using a text message at any time without any further consequences. If the mother was willing to meet one week after being contacted, the day was set for the interview and the mother chose the place for the interview. One interview took place in the hospital at the maternity ward because the child was ill and was still being treated in the NICU. One interview was carried out in the university and the other 23 at the mothers' home. For details of the recruitment process, see original publication 1.

Study 2 participants were midwives (n=20) who worked in the university hospitals of Kuopio and Oulu and had experience in recruiting mothers for placental perfusion studies. The contact persons in the hospitals were the head nurses of a total of five wards. The research project was introduced during a ward meeting, and the wards were provided with fact-sheets about the research along with the researcher's contact details. Seven midwives from Kuopio and thirteen midwives from Oulu volunteered to be interviewed. More information is presented in original publication 2.

Study 3 participants (n=23) were international researchers with experience in human placental perfusion studies. Data were collected from focus group interviews and an open-ended questionnaire in English. Two of the researchers´ focus interviews were conducted during an international seminar held in Kuopio, and one was arranged after the seminar. Before the seminar, an e-mail was sent to the participants informing them of the possible interview. Verbal information was also given before the interview. Focus-group interviews were arranged in a private room. The questionnaire was sent by e-mail to researchers and research groups known to carry out human placental perfusions. Since the first round of e-mails produced only 6 responses, a second e-mail was sent to those who did not respond.

At the end, out of 18 research groups, responses were received from 5 different groups, with a total of 14 responses. The questionnaire was also sent to 11 individual researchers, 5 of whom responded. Thus, the total number or returned questionnaires was 19. Eight of the questionnaire respondents also participated in the focus group interviews.

4.1.2 Documentary material in study 4

Study 4 data were collected from applications received by the regional ethics committee in the Hospital District of Northern Savo. The ethical statement was copied from either the application form (years 2004-2005) or from separate statements. A manual search was performed of all the applications sent to the ethics committee during the years 2004-2009 (n=688). The exclusion criteria were: 1) only a blood sample was taken, 2) tissue was taken from a deceased person. After these exclusions, 56 cases remained (Table 7)

Table 7. Data collection in studies 1-4

Study	Study population	N	Method	Time of the study	Amount of data
Study 1	Mothers	25	Thematic interview	2007–2008	324 pages
Study 2	Midwives	20	Thematic interview	2008–2009	351 pages
Study 3	Researchers Part 1	12	3 Focus-group interviews	2009-2010	43 pages
	Researchers Part 2	19	Open-ended questionnaire	2009-2010	81 pages
Study 4	Statements of principal investigators	56	Analysis of documents	2004-2009	1)

1) Amount of data was from few lines to 2 pages ethical statement prepared by the principal investigator

4.1.3 Interviews and themes

The structure and themes of mothers' and midwives' interviews were compiled according to a questionnaire developed in the context of the NewGeneris project, by the group that studied the socio-ethical impact of environmental health research at the Centre for Human Genetics of the Catholic University of Leuven (Belgium) and a related publication (Beauchamp & Childress 2001). Field notes of all interviews were written down during or immediately after the interviews. During the interviews in studies 1-2, more information about the perfusion research was given to the mothers and midwives, in order to help them to express opinions about the benefits/risks and societal meaning of research in general as well as placental perfusion research in particular. The interviews lasted for 60 minutes on average.

The focus-group interviews and questionnaire of the researchers were also structured according to the same themes that were used in studies 1-2 (Table 8). Participants in the focus-group interviews (n=12) represented 7 different nationalities. The interviews lasted about 60 minutes and were interactive. The saturation point was achieved during the third focus group interview, after which no new focus groups were planned.

Table 8. Themes used in studies 1-4.

Theme	Content
• **Recruitment**	• Recruitment situation • Participation in the research • Decision making
• **Informed consent and voluntariness**	• Comprehension of written and oral information • Voluntariness • Realisation of voluntariness • Communication
• **Risks and benefits of the research for participants**	• Meaning, significance and stressfulness
• **Handling and confidentiality of personal data**	• Concerns for preserving privacy
• **Societal meaning**	• Meaning of the tissue research in general • Meaning of science in general • Connection between political decision making and science • Justification for the research

4.2 DATA ANALYSIS

The interview data were written down word-by-word into a database. The transcriptions were compared with the original recorded data to ensure accuracy. The data were analyzed using thematic content analysis, and the answers were grouped and the concepts with similar content were combined to form upper concepts (Graneheim & Lundman 2004, Malterud 2001, Elo & Kyngäs 2007). Simplified expressions were sought from the data (an example from the study 4: "*Purpose of the research is prevention*..."), out of which upper concepts were created (in this case" *health promotion*"). Data of the mothers were analyzed manually. Interview data of the midwives were analysed using the NVivo 8 software, which has been shown to be applicable for research with large quantities of data (Feely et al. 2007, Gottfredsdottir et al. 2009, Everett et al. 2011). NVivo 8 is a software package produced by QRS International and it is designed for qualitative researchers who need deep levels of analysis for small or large volumes of data. Coding data in NVivo 8 involves the creation of nodes. A node is a collection of references about a studied theme; in this study, the nodes were interview themes. In NVivo, the researcher can create different types of nodes during the coding process by reading through references and then categorising this information. Tree nodes were used when data were being organized in a hierarchical structure (Bergin 2011).

In study 3, the interview data and questionnaire data were analysed using the NVivo 8 software. Both data were analysed thematically (Graneheim & Lundman 2004) according to

interview themes and with data triangulation (Foss et al. 2002, Polit & Beck 2006, Lambert et al. 2007). Descriptive words and phrases were transferred into the NVivo system. This process was repeated until no new concepts emerged. The results section presents the opinions that have been selected as providing a diversified description of the discussed topic. The aim was to select a balanced sampling of opinions from all informants.

In study 4, the data were collected manually. The study protocols in years 2006-2009 were read against the exclusion criteria, and if the criteria were not met, the statement was copied. In years 2004-2005, an ethical statement was included into the application form. A separate statement was also allowed. The content of the statements was analyzed for the same five themes as in studies 1-3: recruitment, informed consent, risk and benefits, confidentiality and societal meaning of the research. The statements were read and meaningful concepts and information were grouped under the selected themes, after which thematic content analysis was carried out (Prior 2010). If a theme was addressed in even one sentence, this sentence was included as a statement within that theme. The data were analysed both qualitatively and quantitatively.

4.3 ETHICAL CONSIDERATIONS

There is little research conducted on the ethics of studies involving pregnant women. Most studies have targeted clinical trials in pregnant women where the potential physical harm for both the mother and baby has been the main objective (McCullough et al. 2005, Helmreich et al. 2007, Wild 2007). The paucity of the studies about ethical aspects in placenta and tissue research in this form can be regarded as a justification for the study. Of the various ethical aspects of the scientific process (Vähäkangas 2004, Merlo et al. 2007), especially recruitment, data collection and the choice of research methods were noted in this research design. The interviews of the mothers were the most sensitive of all these interviews: breastfeeding mothers have been mentioned as a vulnerable group in the Medical Research Act (488/1999, 295/2004, 794/2010) although this kind of study did not interfere with the mothers` physical integrity. However, the sensitivity of the situation must be considered carefully. The purpose of the interview of the mothers was to collate the views of the mothers who had donated their placenta for the placenta perfusion studies. It is evident that this type of research can only be performed with this vulnerable group.

It is self-evident that having a baby is a sensitive situation for a mother, and thus the recruitment process was planned carefully allowing time before coming to a decision. The mothers were visited at the hospital one day after their delivery. Before entering the room, nurses asked if it suited the mother to be asked to participate in the research. After receiving some brief information and a short conversation, a written information sheet was given to the mothers. They had 1-2 weeks time to consider their possible participation. Telephone number/e-mail address was given to the mothers so that they could cancel, if they so wished, their participation by sending a text message or e-mail.

The literature (e.g. Beauchamp & Childress 2001) and legislation (Medical Research Act 488/1999, 295/2004, 794/2010) as well as international guidelines (WMA 2011) emphasize that participants should have autonomy in deciding whether or not to participate in a research projects. This means that relevant information must be given to the participants and their competence to make the decision should be evaluated (Beauhamp & Childress 2001, Medical Research Act). The purpose and methods of the research were explained in the information letters and understanding was ensured verbally in all interviews in studies 1-3. The participants were asked to sign a consent form before the interview and they were told that they could withdraw their consent at any time according to the legislation and international agreements (Medical Research Act, WMA 2011).

The interviews of the midwives were done mostly during their work time; four of them were done elsewhere. In the recruitment process, the contact persons were approached by

email, and they in turn asked possible volunteers to attend the interview. All interviews were conducted in a quiet place to ensure confidentiality. The midwives were also told that answering the questions was voluntary. An uncomfortable situation and possible guilt about one's lack of knowledge can been viewed as a risk here. After the interview, the midwives had the chance to ask questions about the interview and talk about their own feelings at the time.

Participants in the researchers´ focus-interviews were recruited in a seminar and by e-mail. Before the seminar, an e-mail was sent to the participants informing them of the possible interview. Verbal information was also given during the seminar. At the beginning of the focus-group interviews, the participants were told that the interview would be confidential. Confidentiality was respected and only code numbers were used after the interviews to refer to the respondents. The questionnaire included a research information letter which emphasized that participation was voluntary. The questionnaire was sent twice, which is a normal procedure (Caminiti et al. 2011). All data was stored in a locked place, first at the University of Kuopio (currently University of Eastern Finland) and later at the Research Unit of the Hospital District of Northern Savo.

Documentary material was collected by two researchers. Statements or application forms were copied and stored in a locked place in the Research Unit of the University Hospital of Kuopio. The content of the documents was read and analysed by member in the research group, and the names of the principal investigators were not mentioned in the discussions between research group members. Confidentiality was also respected in the analysis process to avoid identification of the research group.

The official Research Ethics committee of the Hospital District of Northern Savo has provided a favourable opinion for interviewing the mothers (21.08.2007, 79//2007). Prior to the interviews of the midwives and the data collection in study 4, administrative approval was asked and received from the participating hospitals.

5 RESULTS

5.1 VIEWS OF THE STAKEHOLDERS ABOUT RECRUITMENT AND INFORMED CONSENT

In the placental perfusion studies, recruitment took place at the hospital and was performed by midwives and researchers. All stakeholders in placental perfusion studies were content with the hospital recruitment and regarded it as acceptable. However, there was also frequent discussion in the interviews about the possibility of recruitment before entering the hospital and about providing some information prior to recruitment, e.g. in the maternity clinic.

The fact that mothers were recruited into the placental perfusion studies in the ward before an elective caesarean section and in the delivery room before a normal delivery was seen as problematic by all parties. Haste in the ward and the fact that recruitment occurred during a care procedure was regarded as negative, and midwives pointed out that they tried their best to find time for recruitment. Mothers noted that having enough time to familiarise themselves with the research and obtaining adequate information about the operation and the research from a familiar nurse were factors that enhanced positive feelings at the recruitment time. The researchers also thought that the recruiter should be someone who knew the situation in the ward and had sufficient information about the research. There were other aspects that also affected the recruitment situation for the mothers, for instance, allowing sufficient time to be spent with nurses. Generally, the lack of concerns in life increased contentment and peacefulness. Regardless of the fear and nervousness of the approaching labour, all the mothers were satisfied about their participation in the placental perfusion research and regarded it as important.

Mothers who were recruited in the delivery room and the midwives doing the recruiting described the recruitment situation especially in the delivery room, but also sometimes in the ward, as challenging. Both groups thought that the mother was experiencing intense emotions such as fear and pain. This was due the delivery itself, the hurry in the ward as well as worries about the baby. The recruitment situation was thus considered as being far from restful. The mother's nervousness was described regardless of the mode of delivery. This sentiment was created by the novelty of the situation, the inability to concentrate, and the lack of information about both the operation and the research. All stakeholders in placental perfusion studies described hurry, e.g. for mothers this was interpreted as nurses waiting for the signature by the bed and an inconvenient situation overall. The midwives agreed with this although they had tried their best to provide time for the mother to make a decision.

Mothers considered their participation in the perfusion studies as being voluntary, which was also confirmed by the midwives. According to the mothers, the main reason for this perception was the way midwives explained the research to them and made clear that their participation was completely voluntary. There were other factors that promoted voluntariness: sufficient time to read the information leaflet, privacy and lack of any financial benefits for the participants. From the mothers' point of view, voluntariness meant that the decision was not influenced by persuasion but it was the participant's own decision and they felt right about it. It was also important to them that the decision would not affect their care in the hospital. Providing information in a way that was intelligible to the participants was also important: understandable language was considered as a part of voluntariness.

Donating the placenta was something that the mothers decided on their own, without discussing it at recruitment time with their spouse or the midwife. In general, according to

the midwives and mothers, there was not a lot of discussion about the study. Both midwives and mothers pointed out that mothers gave their consent almost immediately. Midwives had the impression that the mothers did not thoroughly consider the implications. Most mothers did not ask any questions, and those who did, asked only some basic questions like where the placenta went and how it would be used. Those researchers who were recruiters regarded the information more accurate if it came from the researcher who knew all the details of the study. Mothers preferred midwives rather than scientists as the recruiters in the placental perfusion study, and midwives were also confident about being the recruiters. The researchers emphasized that they did not recruit in the delivery room. Some mothers regarded the option also to contact the perfusion researchers as important. Some mothers thought that nurses were insufficiently aware of the relevant information of the perfusion study and that the knowledge of the nurses was inadequate to provide them with the relevant information. Midwives agreed that they did not have knowledge about the perfusion studies or research methods in general. The researchers proposed that organisations/research groups should employ trained research nurses/midwives who were familiar with and trained in the used of research methods.

The mothers were of the opinion that there was usually no in-depth conversation between the mothers and the midwives. The mothers felt that the communication was mostly equal, although they had expected more dialogue. The nature of the discussion and the language that was used influenced their willingness to participate in the research. The information provided in the written form was adequate according to the mothers, but they also wished to receive more verbal information from the midwives. Researchers paid attention to the hurry which disturbed communication with nurses. They also wondered whether the nurses' attitudes towards research in the delivery room affected the way they acted in the recruitment situation. Mostly researchers considered communication with hospital personnel as being positive, but this was also something that could be improved in the future. Also, regular meetings and training sessions were seen as being useful. *"Midwives' contribution is absolutely crucial, so I think they should be regarded as partners, rather than "a source" of patients."* All stakeholders were confident that good communication created trust and increased the amount of participation in the research.

In general in tissue research, researchers do not pay attention to the recruitment situation in their ethical statements. After the ethics committee revised their instructions in the year 2006, some more information was added to the statement. Most of the recruitments (about 80%) were done in the hospital during care. Although the recruitment situation was explained in the statements more often after the year 2006, the ethical statements did not include all the detailed information e.g. on how to inform recruiters or whether the recruitment situation was sensitive and the patient was competent. Only if persons without the capacity to consent were involved, was there discussion about their competence to participate and their relatives were asked to became part of the consent process. Furthermore, the most common description of informed consent process only mentioned the request of a written informed consent and the possibility to refuse participation. Voluntariness, the possibility to discontinue the research and the time to be given for invited participants to make their decision were not defined in most of the statements. Examples of expressions by the stakeholders in tissue research concerning elements of informed consent are presented in table 9.

Table 9. Examples of expressions by the stakeholders in tissue research concerning elements of informed consent

Elements of informed consent	Mothers	Midwives	Researchers	Principal investigator
Competence to understand and decide	*"At the same time with the care procedures, I was a bit anxious."*	*"I do not prefer delivery ward as the best place to recruit mothers."*	*"We never see the mother, we always go through these nurses or midwives. They ask them. Well, it's easier for us, but I'm not sure how well nurses can explain the experiment to the mothers."*	Only if persons without the capacity to consent (e.g. dementia) were involved, otherwise not discussed. [1)]
Voluntariness in deciding	*"I have time, no one is standing beside my bed waiting."*	*"Mothers have different kinds of thoughts in their minds, baby, and delivery. It reflects on everything."*	*"Freedom. Respect. Because if they are not willing to donate you cannot force them, you cannot keep asking her why you don't want to donate your placenta to us and all."*	*"It is voluntary and they can withdraw anytime."*
Disclosure of material information	*"I have got the relevant information and I had to understand it, and it is my responsibility to ask."*	*"If mothers do not have enough time, they cannot understand what they are doing."*	*"I implemented a new strategy that involved putting a patient information sheet in every section information pack that got handed out to women that were having a C-section.*	*"Material will be given before delivery in writing and orally."*
Recommendation of a plan	*"I have to know what I sign up for."*	*"We should have more information about how to inform mothers and what informed consent is."*	*"I think that sometimes the oral information is in a minor role; if the mothers don't ask then midwives might not tell them as well about research."*	Not mentioned in the documents [1)]
Understanding of disclosure and recommendation	*"I understood as much as lay people can in this kind of research."*	*"I hope they understand, but I am not sure."*	*"I think that the way HOW you ask and WHEN you ask the permission is very important. The one who is asking the permission should be trustworthy and encouraging, but let the mother make her own decision."*	*"Consent will be asked also from a relative if there is doubt that the patient does not understand."*

Table 9. Continued.

Decision in favour of a plan	*"I did not discuss it with my husband, he heard that I will donate the placenta, we did not talk about it."*	*"I hope decision is truly informed, there should be enough time. It depends on nurse also."*	*"I think it's the mother's responsibility to get agreement with her husband or her family members because in my culture families are whole, so we should contribute in every important decision. Or every family member should contribute to make the decision. So to me if we can get the consent of the mother that means we get the consent from her family. "*	Not mentioned in the documents [1)]
Authorization of the chosen plan	*" I gave my placenta to the research, I signed the paper, commitment and fair play (mother and researcher)."*	*"I tell to the mothers about the research and signature is included the protocol. I leave the papers, mother can sign later."*	*"So it is not the mother just signing, "Yes, take the placenta" but no, we need information from her to be included in the studies or research."*	*"They will be asked to sign the consent."*

1) Not discussed in the analyzed statements

5.2 VIEWS OF THE STAKEHOLDERS ABOUT RISKS, BENEFITS AND CONFIDENTIALITY

The most important point raised by the mothers under the risks and benefits theme was the reliability of the research personnel in placental perfusion studies. All mothers had read the information leaflet and they pointed out that having the University and professors involved in the research conferred reliability to the situation and made participation easier. Placenta research, as well as other tissue research by the principal investigator, was not seen as a risk for the participants. Mostly, the samples were considered as waste and therefore no risk was seen. *"This is important research; I do not get any specific benefit for myself (Mother)."*

According to the interviewed mothers, they did not know the details of the placental perfusion studies. The midwives were also concerned about their own knowledge of the research, methods and scientific research in general. The lack of respect from scientists was also a factor that was bothering midwives. Researchers acknowledged the need for providing information to the midwives, and in some places regular meetings had been organized. The mothers as well as midwives and researchers understood that the general knowledge achieved from placenta perfusion studies may be distressing and might make mothers feel guilty of their lifestyle. *"I cannot think of any risk at all, maybe guilt (Midwife)."*

The proposed benefits for the mothers included the possibility to receive informed counselling regarding, for instance, medication and substances that were harmful for the foetus. The importance of health promotion was also emphasised as a benefit. The risk to midwives was seen by the researchers in the increased workload. *"The burden to the mothers is limited, but the nurses may think it is a burden when they are busy (Researcher)."* In addition,

the midwives' actions when handling the placenta was seen as a risk for the validity of the tissue material. "*Sometimes you can see that they handle the placenta quite roughly (Researcher).*"

The researchers mentioned that the potential harm may come from working with infectious material, e.g. HIV, hepatitis or other infectious diseases. They thought that special precautions should be formulated as a written guideline for work with placental tissue as potentially infectious biological material. In addition, the future use of samples was considered a potential risk or harm to the mother if her identity was not protected. This was mostly connected to biobank research. Generally in tissue reseach, the researchers did not regard the use of waste sample in research as a potential risk for the participants. Risks and benefits were explained quite well in over 80% of the statements. In all statements, the difference between research and care was left unexplained and disregarded by saying that tissue donation was voluntary. *"The issue of bio-banking. Should that tissue be retained or should the tissue be burned and disposed of after the study has been done (Researcher)."*

The samples were anonymized for the placental perfusion study, which was considered as safe by the midwives and mothers who donated their placenta in the research. There were also mothers for whom anonymity was not important in this kind of scientific research and who would have liked to have more information about their own placenta. The mothers' trust in the confidentiality was dependent on how well the verbal and written information about data processing was given to them. Clear and informative written information with the names of the researchers also created trust.

The researchers pointed out that in their studies, they acted according to the laws and regulations about confidentiality, but in practice it always depended on the communication between the recruiter and the mother in determining how well the mother understood confidentiality. It was considered challenging to inform mothers of the future use of samples and their storage e.g. in biobanks in a way that the mothers understood how their personal information would be handled. *"Identification is not needed if we only study basic perfusion and perfusion of different medical products and placentas are from normal uncomplicated pregnancies. Identification is needed if the obstetric factors are evaluated with the placental perfusion capacity (Researcher)."*

In the ethical statements, researchers explained the handling and confidentiality of personal information in over half of the cases. Coding was correctly explained in 51.8% and anonymization in 8.9%. In these cases, coding and anonymization were defined so that it was clear for the reader what the author meant by these terms. However, in 3/56 statements, the meaning of anonymity (no possibility to link data to a person) and coding was confused. Half of the cases contained information about who possessed the code key, and 32.1% explained how the data will be stored.

5.3 VIEWS OF THE STAKEHOLDERS ABOUT SOCIETAL MEANING OF TISSUE RESEARCH AND SCIENCE IN GENERAL

On the basis of the analysis done, when combining data from different papers, the societal meaning of tissue research could be clarified by the following themes: scientific knowledge, image of science and research ethics. (Fig 1)

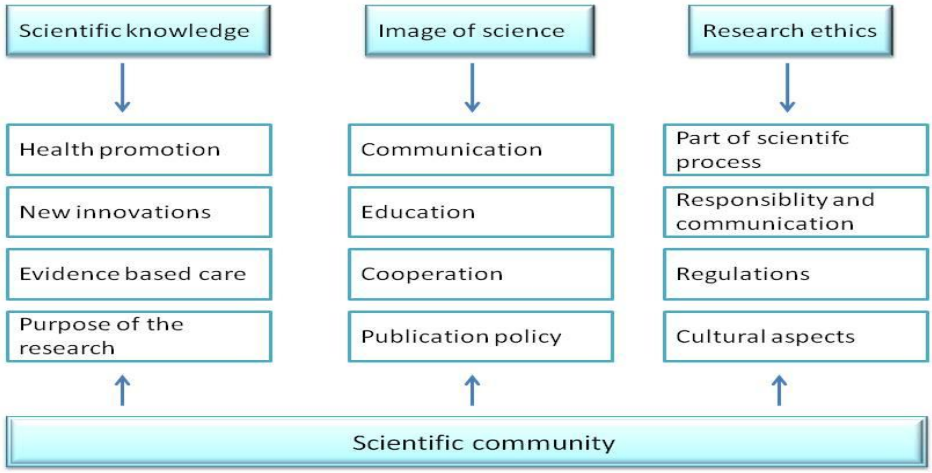

Fig.1. Elements of societal meaning given by different stakeholders

Scientific knowledge

Scientific knowledge which benefits society as a whole was seen as important by all stakeholders. According to the researchers, tissue research can be useful for public health e.g. in clarifying disease mechanisms and providing possibilities for preventive actions and better care. Placental perfusion research was also seen as useful to the society in many ways by all stakeholders. They agreed that research would promote the health of children by helping to formulate new guidelines for pregnant women and in that way to promote children's health. Especially mothers and midwives clearly expressed the wish to have information which was based on science and not on assumptions. Furthermore, most mothers and midwives had a positive image about biomedical research in general. "Too much knowledge is painful" was a frequent comment among the midwives and mothers about scientific research. Although they trusted science, they also perceived threats which were worrying or even frightening to them. Their concerns and fears were related to the question of where to draw the line in science: what did you have the right to study and what not, what could you interfere with, and what could you change in people. Midwives were also concerned about the question of financial and academic interests: was the research project commercial, did the researchers only wish to add to their own scientific merits, or was the participants' point of view also being taken into account. These questions revealed critical views about science, and the respondents contemplated issues such as research frame, methods and the benefiting parties. They were concerned about research on genes and stem cells because they did not possess enough information about such topics. In general, however, medical research was highly appreciated by mothers and midwives and its benefits to individuals and society as a whole through health promotion were emphasised.

According to the researchers in the placental perfusion study and the principal investigators in tissue research, new innovations and usefulness of the research were one of the main factors driving scientific endeavour. The mothers clearly expressed that they were willing to donate tissues to be used in biomedical research and thought that it was better to use human tissues than laboratory animals. Mothers hoped for new innovations in drug development. The possibility to prevent diseases rather than treat them was also expressed by the mothers. Mothers thought that the usefulness of science in general depended on the purpose of the research (Fig.1.)

Image of science

Aspects of societal meaning included the scientists' responsibility for the image of science both to the public and to policy makers. Communication e.g. with policy makers and research participants was seen as a key to creating a well-informed society. The midwives and mothers thought that politicians and researchers should cooperate, create networks and pay attention to informed decision making. They were concerned about money having more influence on political decisions than scientific knowledge. It was also emphasized that science should be independent and unaffected by political and religious factors. Midwives, mothers and researchers felt that researchers had a responsibility to publish their results in such a way that political decision makers and the general public could find and understand them. According to their opinions, significant results were based on the skills of the researchers and reliable partners such as universities and university hospitals, which were also factors in creating trust. Education also created a sense of reliability. They also discussed the motives behind the work done by the researchers (whether just for their own career or mixed with benefits to society). One interesting detail was that they also wondered how researchers would deal with unexpected results. Midwives were also confident when the research organization was trustworthy. Reliability was further increased if midwives knew the research group (Fig 1.)

Research ethics

According to the researchers in placental perfusion studies, ethics is becoming an increasingly important part of the scientific process, and researchers have to deal with such questions on a daily basis. Some researchers stated that there needed to be a balance: not to encroach on the participant's basic rights like privacy but also not to create too much protectionism as an obstacle to hinder research. This kind of balance is necessary for the benefit of research to society as a whole. Researchers also expressed doubts about whether some policies, for instance the handling of applications in research ethics committees, were too strict for basic research using human placenta, considering that placenta is generally viewed as waste in Western countries. The recruitment process was emphasized by the researchers because they find placenta difficult material to work with, and consequently a large number of placentas are needed. A good recruitment process is therefore important to obtain enough tissue material and improve the quality of the perfusion study. Communication was seen as being essential by the researchers to inform society and policy makers in order for them to be able to formulate sensible research ethics policies that will protect and respect the patients' interests without making research more difficult than necessary.

Researchers pointed out that they took full responsibility for the ethics in their research projects. Midwives noted that commercial research using human placenta could be problematic: on the one hand, the products of the pharmaceutical industry would benefit everyone, but on the other hand, exclusively commercial purposes were regarded as being negative. They believed that even commercial research should benefit society in some way. It was a common opinion that placental research that was being conducted as placental perfusion did not have any ethical problems if the mothers were informed about the research and they gave voluntary, informed consent. It was the general opinion among mothers and midwives that mothers were able to decide whether to donate their placenta. In Finland, hardly anyone has an emotional or cultural bond to the placenta. International researchers have disclosed cultural meanings more clearly and in contrast to the situation in Western culture, family or community consent may be required. One important aspect of these cultural factors is that the educational level of the donor needs to be addressed. (Fig 1.)

6 Discussion

This is the first study comparing views of different stakeholders in placental perfusion research. Only one study on the views of the mothers and fathers in human placental perfusion has been published by Lind and coworkers (2007). Although there are publications on the ethical aspects of tissue research, none were found systematically analyzing the ethical statements of scientists. In addition only a small number of studies concerning the views of nurses/midwives participating in biomedical research was found.

An important finding in this study was that mothers as well midwives, when rightly informed about the purpose of placental perfusion studies, were very interested in the studies and supported the use of placenta. The results of this study also indicate that they do not perceive any ethical problems or risks related to the scientific use of human placenta for anonymous pharmacokinetic studies. This was in accordance with the opinions of the researchers involved in placental perfusion studies.

The Research Ethics committee of Hospital District of Northern Savo requires that a separate statement about ethical aspects is provided by the leading researcher which is also in accordance with the recommendation of TUKIJA, The National Committee on Medical Research Ethics (TUKIJA 2012). An interesting and important aspect of the results was the insufficient handling of the key ethical aspects in many of the applications submitted to the research ethics committee. On the other hand, only the official forms and separate statements sheets about ethical aspects were studied and it is possible that the research plan in some cases included ethical aspects.

The discussions about the selected themes with different stakeholders and the analysis of the ethical statements revealed several ethical aspects of particular interest in tissue research. On the basis of this, following aspects will be discussed here: aspects of the informed consent process, collaboration with different stakeholders and education, confidentiality, risks and benefits as well as societal aspects. One important outcome of this study was the identification of several critical points about the informed consent process of tissue research in a clinical setting. The most obvious gaps identified in the process were the conceived insufficient interaction between the researchers and nurses/midwives as well as between the recruiters (midwives or researchers) and the research participants. In some cases, the time for the decision process available for the participants was regarded as too short. On the whole, researchers should consider more carefully the recruitment and informed consent processes and the ethical aspects of their research. (See Fig. 2).

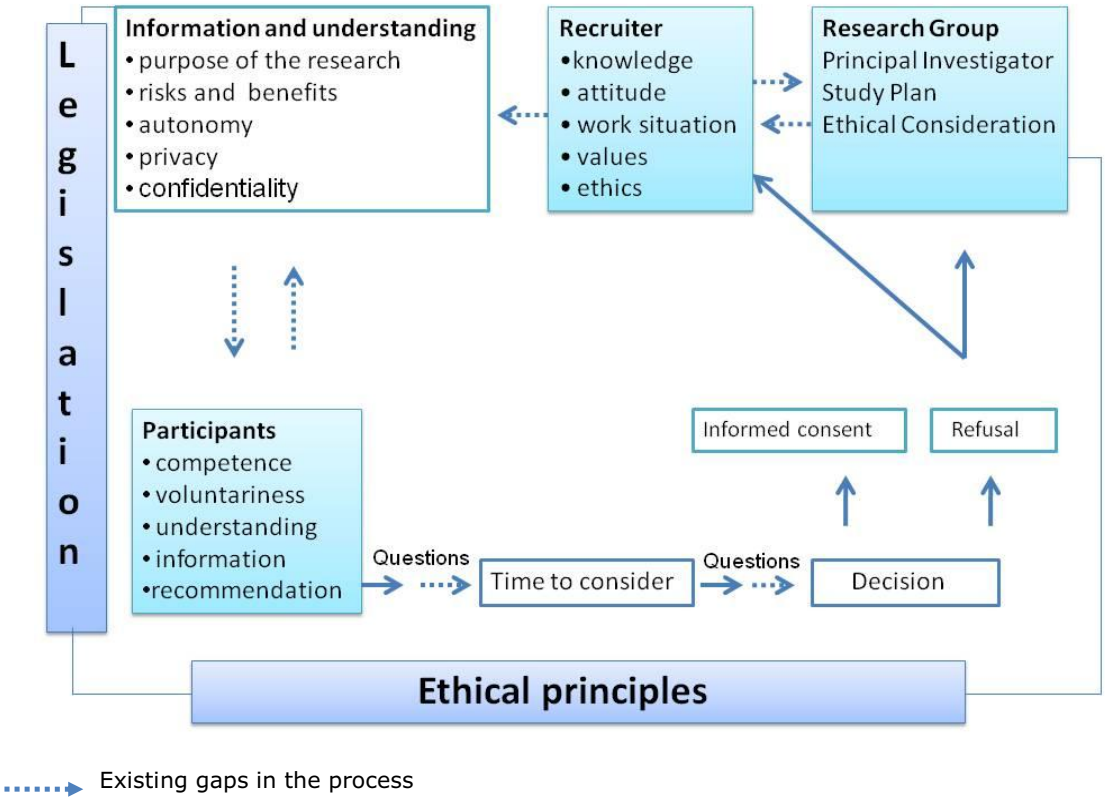

Fig 2. Aspects of the informed consent process as emerged from this study

6.1 ETHICAL ASPECTS OF INFORMED CONSENT AND RECRUITMENT PROCESS

In the literature the complexity of informed consent process has been described in various contexts (e.g. Mason et al. 2000, Hunter 2006, Kass et al. 2007, Länsimies-Antikainen et al. 2007, 2010a,b, Halila 2007, Parvizi et al. 2008, Wendler & Grady 2008). An aspect of our study, not much discussed in the literature, is the comparison of the views of the different stakeholders in particular projects. This has allowed a more holistic view of the informed consent process (see also Beauchamp & Childress 2001, Vähäkangas 2004). Also this is one of the first studies on the views of different stakeholders in tissue research. (Fig.2).

In accordance with the literature we found that understanding of research information is limited among research participants (Crepeau et al. 2011, Desch et a. 2011, Monson et al. 2012). There is a consensus in the literature that research participants may totally misunderstand clinical trials in which they agree to participate (Jefford & Moore 2008, Schwartz & Appelbaum 2008, Wendler 2011) and they may have difficulties in remembering the actual signing situation (Hamilton et al. 2007, Falagas 2009). In our study based on the thorough interviews, it became clear that the comprehension of the study itself was difficult to keep in mind (I,II). The mothers in general could not remember the purpose of the study, until they were reminded during the interview, although all but one of the mothers remembered that they had signed the consent form. Therefore, it was surprising that the analyzed statements on ethical of the scientists (IV) included very little information

and considerations about the recruiting in clinical settings and the associated ethical aspects. In earlier studies (Länsimies-Antikainen et al. 2010a,2010b, Lynöe et al. 2004, Hamilton 2007, Behrendt et al. 2011) it has been shown that it is important to consider the actual situation when the signature is gathered from the participants. In general, timing has been considered as being an important aspect (Vähäkangas 2008, Hamilton et al. 2007). This theorical understanding is contributed by a limited number of studies on how much information the research participants comprehend (see e.g. Crepeau et al. 2011, Desch et al. 2011, Monson et al. 2012). Manson & O`Neil (2007) have emphasized that signing the consent should fulfill legal as well as ethical requirements. Therefore the consent process should not be only formalized routine and regarded as protection against liability, but resulting with a true honest aim to understand the informed consent and the study.

All stakeholders in human placental perfusion studies considered the delivery as a very sensitive situation with emotions ranging form joy to fear (I-III). It is well-known that strong emotions may impair understanding of the given information (Helmreich et al. 2007, Vernon et al. 2006) as also shown in this study. It is also well-known that obtaining an informed consent in an ethically justifiable way from women close to labour (Dorantes et al. 2000, Vernon et al. 2006) or even generally in clinical settings (e.g. Cahana & Hurst 2008, Hewitt et al. 2009) is challenging. In accordance with the literature found that understanding of research information is limited among research participants (Crepeau et al. 2011, Desch et al. 2011, Monson et al. 2012).

This study showed also that some midwives considered participation in the recruitment process problematic in practice, especially if the clinical work was hectic. Nevertheless, the delivery room was seen as an adequate recruitment location for placental perfusion studies by both mothers and midwives. Both the midwives and mothers told that the participating mothers tend not to ask questions about placental research, which may be explained by the fact that placenta is generally considered as waste after delivery. Nonetheless, both groups (I, II) regarded dialogue as beneficial in providing relevant information to the mothers. Personal interests in science of the midwives also affected the manner in which they provided information (II) which is accordance with earlier study (Potter et al. 2009). Those who expressed interest in science were willing to learn more about recruitment as well as research in general. All in all despite the challenging circumstances in the delivery room or in the ward and the concerns expressed by the midwives, it was a general feeling by all stakeholders that the mothers' decision to participate in the perfusion study was a voluntary choice although in some cases time for decision was regarded as too short.

Recruiting during delivery was discussed during the interviews. Indeed, there were general consensus that recruitment should take place during early labour and this also has been pointed out in the literature on the view of mothers (see e.g. Vawter et al. 2002, Lind et al. 2007). Vawter and coworkers (2002) stressed that the recruitment for research must take on account the ability of the mothers to receive information and therefore, to ensure understanding it would be important to repeat the information about the study after delivery. These findings call for amendments to be made in the practices in placental perfusion studies and stressed the importance to carry out this kind of project. In individual research much more could be done than currently is the case to study the practical ethics concurrently with the actual studies. It is also evident that more research is needed on the points of view of participants, and especially midwives or nurses in placental studies.

However, most researchers in placental perfusion studies were content about the recruitment process in their organizations (III). It is noteworthy that in the ethical statement the scientists did not point out the putative ethical aspects of the actual signing situation, and only a few of the studied statements discussed how the competence and understanding of the participants would be ensured. Moreover, in these statements voluntariness was usually mentioned only very briefly in one sentence (IV). In this study the researchers (III) also noted this as a possible problem and pointed out that in Western thinking, the placenta is mostly considered as waste. Some researchers suggested that current guidelines and

processes for obtaining informed consent should be reviewed also from a cultural perspective. Research into the validity and user friendliness of information sharing procedures to obtain the consent in different cultural settings would be very beneficial (Bhutta 2004, Jenkins & Sugarman 2005). This indicates that opinions of all stakeholders are very crucial when improving the recruitment situation in order to take on account the multidimensional aspects of the consent process.

In this study, mothers were interested to know about the research in which their placentas would be used since benefit to others was the reason why they had decided to donate the placenta. Also Lind and coworkers (2007) showed that mothers who donate their placentas to the perfusion studies were interested in the purpose of the research, and the reason for donation was beneficence for society. This has been pointed out also in other type of tissue research, by many authors (see e.g. Hansson et al. 2006, Hemminki et al. 2009, Hens & Dierick 2010, Morrell et al. 2011).

In conclusion there has been intense discussion about the form of informed consent in scientific research in the literature during the past few years (Van Diest 2002, Savulescu 2002, Aromaa et al. 2003, Knoppers 2004, Vähäkangas 2004, Hansson et al. 2006, Hunter 2006, Wendler 2006, Hansson et al. 2007, Hamilton et al. 2007, Cahana & Hurst 2008, Schwartz & Appelbaum 2008, Hewitt et al. 2009, Hofmann 2009, Secko et al. 2009, Toccaceli et al. 2009, Budin-Ljøsne et al. 2011, Wendler 2011, Stjernschantz Forsberg et al. 2009, 2010, 2011). In particular, there is growing support for a broad consent (also described as open, generic or blanket consent) in tissue research, particularly in biobank research (Kaye 2004, Hansson et al. 2006, 2007, Stjernschantz Forsberg et al. 2009, 2010, 2011). One justifying reason for this situation has been the belief that research participants generally do not want to know the exact purpose of the research where their tissues will be used (Stjernschantz Forsberg et al. 2009, 2010, 2011, Treweek et al. 2009). On the other hand, in the future, it is predicted that there will be increased awareness of the rights of participants to maintain control over their samples or personal information (Kaye 2004, Hofman 2009). It is noteworthy that the discussion about the form of different consent applies only to propositions for the form of consent but not acts of consenting and decision making process. According to Manson & O´Neil (2007) more important is good communication between different stakeholders. Therefore an ethical discussion about the way that informed consent has been obtained, especially in terms of ethical rights, needs to continue (see e.g. Takala 2004, Vähäkangas 2004, 2008, Manson & O´Neil 2007, Tupasela et al. 2010).

6.2 COLLABORATION WITH HOSPITAL PERSONNEL AND EDUCATION ABOUT ETHICAL ASPECTS

The results of this study show that researchers, as well as other stakeholders in placental perfusion studies, considered communication between all stakeholders as being extremely important (I-III). Good communication was linked not only to successful recruitment and informed consent process, but also to voluntariness to participate, confidentiality and societal meaning. Communication is an aspect which has also been known to clearly affect the success of human recruitment in general (Hietanen et al. 2007, Länsimies-Antikainen et al. 2010b). Researchers (III) pointed out also a practical reason for enhancing good communication: to obtain enough placentas and in this way to promote the quality of the research.

A major ethical issue is how to educate the recruiters when they are not part of the research group i.e. how to best inform nurses/doctors about the research in such a way that they can provide relevant information to the participants. The studied researchers (III) considered training of the hospital personnel as being essential in order to provide the best possible information to the mothers donating their placentas. They thought that this guidance would also improve the informed consent process, in agreement with the existing

literature (Brown et al. 2007, Hietanen et al. 2007). Nevertheless this aspect was missing in the ethical statements of most of the scientists, when the recruiter came from outside the research group. Furthermore, previous studies (Lavori et al. 2007, Jerosch-Herold et al. 2011) have observed that even if planning is done carefully and information is given to the recruiters in practical terms, the recruitment in practice can be very challenging as shown also in this study.

In placental studies, it is rather common to use midwives as the recruiters (Audette et al. 2010). According to this study, the midwives in university hospitals considered research to be an important part of their work and in principle they were happy to serve as recruiters and work with different research teams. There is a conflict in this situation i.e. on one hand mothers prefer that midwives act as recruiters but on the other hand midwives cannot have access to all the details about the study that mothers might wish to know. According to previous studies nurses feel that they do not have enough understanding of various methodologies and the general issues inherent in scientific research, and thus more education is required (Kuuppelomäki & Tuomi 2003, Peter et al. 2004, Kuuppelomäki & Tuomi, 2005, Roxburgh 2006, Merry et al. 2010). In spite of the information being given to the midwives, only one of the 20 midwives felt that she had good knowledge about placental perfusion research and 12 stated that they had an unclear idea about the purpose of the research. The fact that the wards are large with many nurses and with continued changes to staff makes it difficult in practice to keep everybody in personal contact with the researchers. It would be important in the future to find the best ways and situations to educate the nurses about all of the research on-going in the maternity wards. One such forum could be a webpage where the information would be given in detail. However, this would then require the management to convince the nurses to take the time to visit the page (Merry et al. 2010). In the training of staff in university hospitals these kinds of instructional possibilities should be utilized more but this is naturally dependent on the availability of resources. It has been discussed in various research contexts i.e. who is the best recruiter of participants for scientific projects in biomedicine and health (e.g. Donovan et al. 2003, Mapstone et al. 2007). It is evident that researchers know the project thoroughly, but, the intense need to gather participants may lead to coercion (see e.g. Sugarman et al. 1999). Interestingly, Donovan and coworkers (2003) have suggested that recruitment for clinical trials could be carried out by nurses as effectively as doctors as and more cost-effectively than recruitment by doctors.

In general, and in accordance with earlier studies (Sale 2007, Merry et al. 2010) the nurses interviewed here felt that their work as the recruiters of participants to scientific research had gone unacknowledged. The midwives felt that sufficient information would also motivate them to recruit more efficiently and better. Researchers (III) expressed some concerns about the ability of the midwives to provide accurate information about the complex research model and the aims of the studies. This opinion was also supported by the information provided by the mothers (I). The researchers (III) suggested that midwives should be part of the research team acting as research nurses to ensure the flow of information and good communication. However, extra resources would be needed for research nurses or midwifes. Moreover, organizations should also provide leadership in support of responsible practical conduct of research (see e.g. US National Research Council 2002).

In summary, ensuring good communication with different stakeholders would improve the quality of research by avoiding at least some technical and ethical failures. This matter should be taken into consideration in study plans and be transmitted to funding agencies. It may well become a requirement that there is funding to support additional staff like research nurses or midwives is included not only in grant requests for clinical studies but also for experimental studies with human tissue such as the placenta.

6.3 ETHICAL ASPECTS OF CONFIDENTIALITY, RISKS AND BENEFITS

Confidentiality of the research is a basic legal and ethical requirement that has been emphasized in many international guidelines, e.g. the Declaration of Helsinki and in national legislation, e.g. the Finnish Medical Research Act, Act of Medical Use of Human Organs and Tissues and Personal Data Act. In the literature, confidentiality has been raised as an important factor in the field of tissue research, because of the possibility of accessing genetic information (Hull et al. 2008, Tännsjö 2011, Ursin 2010). In this study the meaning of confidentiality in placental perfusion studies to mothers and midwives was less significant. According to the thematic interviews of the mothers and midwives, it seemed that confidentiality of personal information was not important to the mothers (I,II). Mothers also regarded their privacy being respected which is in accordance with the earlier study by Leino-Kilpi and coworkers (2002). One reason for the opinions of the mothers may be that the perfusion studies carried out with their placentas were not genetic research. They probably did not know that placenta and cord blood could be used also in genetic studies. In many perfusion studies, including the studies with their placenta, the placenta is anonymised prior to its use in the study. After anonymisation, it is impossible to provide personal specific information of the function of their own placenta to the mothers although they have wished for this information. Mothers studied here did not regard anonymity of the placentas being as important; a more important for to them was the potential benefit to the children and society (I).

Approximately 64% of scientists considered confidentiality in their statements to the ethics committee (IV). The others may have explained confidentiality in the research protocol or some may not have considered confidentiality as an ethical issue. Furthermore in the literature the terminology might be confusing, for instance the definitions of anonymity and coding are poorly defined (Vähäkangas 2004) which also was the case in some analyzed statements. It is clearly challenging to make the studies understandable to lay people and some details may even be confusing both to scientists and the participants. Thus the scientific community should pay attention to clarification of scientific terminology, which actually may be regarded also as an ethical requirement in human studies.

The so-called therapeutic misconception, which means that the participant thinks that the study is part of the treatment, is regarded to be a common situation in clinical studies (Lidz et al. 2004, Appelbaum & Lidz 2006). This kind of misunderstanding can easily occur when the recruiter is the patient's own doctor or recruitment is performed during clinical care. The ethical issue here is how to explain the difference between medical care and research to the patient. This consideration was missing from the ethical statements of the scientists (IV), even though 80% of the studies were dealing with tissues being removed as part of clinical care. Probably, many scientists simply regarded the leftover tissue sample as a waste, and no concern for the patients, and therefore they had not discussed the matter in ethical statements. It is noteworthy that a failure to recognize the difference between scientific research and ordinary medical care negates the ability of a potential participant to provide a meaningful informed consent (e.g. Hofmann 2009). Moreover, it has been lately discussed whether the distinction between research and medical practice is already too strict (see e.g. Beauchamp 2011, Hansson & Chadwick 2011, Largent et al. 2011). Additionally, it has been discussed whether the type of tissue research e.g. the invasiveness of the procedure, autopsy specimens, healthy volunteers (see e.g. Vähäkangas 2004, Kapp 2006, Gillet 2007, Tassé 2011) should influence the ethical evaluation process. Also in this study, some researchers in the interviews and questionnaire called for a balance between protecting the participants' basic rights like privacy while keeping research procedures free of unnecessary obstacles.

In this study, the researchers stressed that the research on placenta involved no physical risk to the mother and the baby and thus there were minimal ethical dilemmas from that

point of view. Some burden to nurses was perceived, such as the extra work (see e.g. Sale 2007). The researchers thought that mothers might perceive as a risk some type of guilt related to their own lifestyle, e.g. smoking, a finding found in the opinions of both the mothers and midwives. The future use of the placentas was regarded as a potential problem if confidentiality was not protected by the researchers.

Even though the mothers did not consider confidentiality as important, it is evident that confidentiality will become one of the important factors in biobank research like stated in Government Bill of Biobank Law (see e.g. HE 26/2011). It will be challenging to explain the concept of confidentiality of the data for research participants, especially whether they are giving consent for a certain study or providing a broad consent. However, this is an important point if one wishes to obtain a truly informed consent from the participants. (See fig. 2).

6.4 SOCIETAL MEANING OF SCIENCE

The importance of societal meaning of the scientific research was considered as significant; especially the scientists stressed this point in their ethical statements (IV). Also stakeholders in placental perfusion studies regarded science as significant for promoting health and developing new innovations (I-III). In this study both mothers and midwives expressed their trust in science. It is well- known that Finnish people consider science to be a trustworthy activity, especially medical science and the work done in universities (Hemminki et al. 2009, Finnish Science Barometer 2010). Finns also trust in the regulatory authorities such as research ethics committees (Special Europarometer 2010). The midwives were asked about the meaning of science in general, and they considered scientific information as being important. This has been noted also in other countries (Meah et al. 1996, Peter et al. 2004). The midwives mentioned stem cell and genetic research as examples of areas of concern, because they considered these areas as unfamiliar. They were unaware of the fact that placenta and cord blood are important sources for stem cells (Locatelli and Burgio 2002) and they expressed no concern about the use of placenta in scientific research in general. On basis of this, in the future attention should be paid especially on the education of midwives and on the information provided to the recruiters by the research groups. Furthermore, it should not be taken for granted that lay people are willing to support scientific biomedical research. Participation in research e.g. by donating tissue samples, is based on trust and this has to be gained and retained if scientific research for biomedicine to thrive in our society (Merlo et al. 2007). There is a consensus in the literature that the future of the research is dependent on trust (Merlo et al. 2007, Savulescu 2002) and education of the general public is the key to enhancing trust in research involving human tissues (Savulescu 2002).

Based on the analyzed data the societal meaning of tissue research was perceived as a multidimensional topic, ranging from the creation of new knowledge to enhancing the capability of the scientists to communicate with the public (I-IV). Scientists involved in placental perfusion studies were of the opinion that research on placenta will increase in the future (III). All stakeholders in the placental studies regarded active communication as imperative for informing the public in addition to the scientific community of the results obtained, which in turn is beneficial for the development of the method (I-III, see also Lercher 2010). Researchers also pointed out that ethics is becoming an increasingly important part of the scientific process, and researchers have to deal with such questions on daily basis. It was notable that in the interviews of researchers, Campbell and coworkers (2008) found that ethical aspects were not considered in the day-to-day decision making by professionals in the research. Therefore they pointed out that greater attention will need to be paid on ethical training and debate.

The guidelines of the Ethics Committee of the Hospital District of Northern Savo state that researchers must consider the justification for the research in their ethical statements. Furthermore, the Declaration of Helsinki, as well as other guidelines and regulations, require that research should be based on earlier literature and this should appear in the research plan (WMA 2011). One of the most important justifications for doing biomedical research is its benefits to patients in the form of improved patient care i.e. acquiring knowledge for diagnostic, therapeutic and prognostic purposes. Nonetheless, the studied statements (IV) contained little information about the societal meaning of the proposed research. Similarly to confidentiality, societal justification is a topic that may not be perceived as an ethical aspect, and this may have been described in the research plan. It was common for the researchers to simply repeat the research protocol in their statement, which in many cases did not include the justification. It was noticeable that the ethical statements were more structured in 2006-2009 than in 2004-2005. By 2006 the ethics committee had already formulated the requirements for the details that needed to be included in the ethical statement. Thus, in this study although the formal requirement and advice from the ethics committee had a positive effect on the written statements, it is still unclear how ethics instructions should be given (see e.g. Anderson et al. 2007, McCormic et al. 2009, Antes et al. 2010). This is in accordance with the call for more training among scientits to acquire the capacity and knowledge for deeper understanding of the ethical aspects of research (Faber et al. 1992, Mertz et al. 1999, Paul 2000, Taylor et al. 2008). In earlier studies (Mertz et al. 1999, Keinonen et al. 2001, Bueno et al. 2009) it has been shown that most of the clarifications requested from the researchers by the committees dealt with the informed consent process. Therefore, knowledge and education about research ethics is needed and experience about research should be initiated as early as possible, for example in courses to undergraduates like Faber and co-workers suggested already in 1992. It would be helpful to both the scientists, and nurses, if ethical concepts like voluntariness and informed consent were to be clearly explained in practical manner in educational courses (see e.g. Appelbaum et al. 2009).

The fact that ultimately it is the scientists who are responsible for the good ethics of their research was also noticed in this study by the scientist. Otherwise there is a general consensus in the scientific community that scientists themselves should consider ethical aspects as an integral part of the research process (Grandjean & Sorsa 1996, Vähäkangas 2004, Wendler 2011). The demands that certain types of research require less information to the participants or a different kind of consent as well as lighter ethical review process may be problematic. It has been stated that self-regulation of the scientists is not enough (see Holm 2011) and questions have been raised about the best way to perform this assessment. It will be challenging to develop an informed consent process that is valid for future studies in which the samples may be reused (see table 2 requirements of legislations in Finland i.e. Act of Medical Use of Human Organs and Tissues). Especially how confidentiality is ensured in megastudies is unclear. For instance, one practical difficulty is that it would be extremely difficult and time-consuming to re-contact all subjects in order to gain a new consent for a reuse in research especially if thousands of people were involved (Petrini 2010 a,2010b, Hansson et al. 2006). These issues can only be clarified by further studies and in discussions about ethical review process and documents.

The interviewed midwives regarded the use of human placentas for commercial purposes as problematic, with the exception of their use for pharmaceutical research. However, the midwives felt that the recruitment for commercial research would be more challenging, because they felt that in such a case, the purpose of the research would need to be clarified to the mother in detail. Earlier studies have reported similar results (Hens & Dierickx 2010, Morrell et al. 2011). Nevertheless, Hemminki and coworkers (2009) have reported that there was no difference in Finnish attitudes about whether research was being conducted by a public or private enterprise. Balancing of ethical benefits and costs (Zwitter

& Colouh 1996) in the commercial use of human tissues in general has been stated to demand much more studies than currently exist (Hemminki et al. 2009).

Although the procedures in some cases did not materialise exactly as planned in perfusion studies, the mothers were still content because they considered the placenta as a waste product and they were satisfied that it could be put to some beneficial use. In Western countries placental tissue is considered as waste after the birth. The interviewed mothers considered that it was their own decision to donate their placenta. However, this may not necessarily be the case in other countries (Jenkins & Sugarman 2005). Researchers in placental perfusion studies stressed that this topic has implications involving also cultural dimensions. In general, the cultural aspects in tissue research have attracted little attention in placental research (Jenkins & Sugarman 2005) or in biomedical research in general (Bhutta 2004, Glickman et al. 2011). Also, it has been stressed that there will be a shift of perspective in biomedical ethics into a more global (Ijsselmuiden et al. 2005, 2008, 2010, Prainsack & Buyx 2011) and towards solidarity (Lev 2011, Prainsack & Buyx 2011) also research with human tissue (Prainsack & Buyx 2011). Latest report of Nuffield Council on Bioethics stress importance of solidarity especially in biobank research (Prainsack & Buyx 2011). Also, WHO (2011) have stressed the importance of selection of study population and community-based considerations in the ethical review process. They have also encouraged researchers actively engage with communities in decision-making in research and being sensitive to respect cultural, traditional and religious practices. However, one must not conclude that cultural considerations must always dictate that members of certain groups' communal autonomy will always take precedence over individual autonomy (UNESCO 2008).

In summary, the societal aspects of science are extremely important and more attention should be paid to this topic in education and science as well as in society at large. Lately, the ethical importance and influences of sources of funding, institutional affiliations and conflicts of interest have been highlighted (WMA 2011). These aspects were missing from this present study. Clearly these topics must be addressed in future studies. The image of science is also dependent on the capability of the scientists to convey the results of their work in comprehensible language to the general public. This will enhance the trust of lay people as well as political decision-makers. The scientific community should not take this trust for granted, and thus the scientist should listen closely the opinions of different stakeholders.

6.5 RELIABILITY OF THE RESEARCH

According to Tong and coworkers (2007) the reliability of a study can be assessed by examining the study design, and by evaluating the analytical process and the findings. The themes considered in the interviews of both the mothers and the midwives were the same to ensure comparability of the results (I,II). The interview themes in the focus groups (III) were also created out of the themes raised in the two previous studies (I,II). The focus group interviews were complemented with a questionnaire whose open-ended questions were derived from the interview themes discussed former studies 1-2. The ethical statements (IV) were analyzed by using an ethical framework which was derived from the interview themes. Due to the data and method triangulation in all four studies, the results can be regarded as an entity, and this enhances the validity and credibility of the study. Triangulation helps to obtain a more complete and contextualized portrait of the phenomenon being studied. Data source triangulation was ensured by using multiple sources of data, i.e. from the mothers, nurses, researchers and documents (see e.g. Polit & Beck 2006) and method triangulation by using different methods (see e.g. Lambert & Carmen 2007) in this study e.g. focus-group and questionnaire for the researchers (III).

As a way of guaranteeing the credibility, participants in the first three studies (I-III) were selected so that they had been involved in some way in placental perfusion studies. All interviews were conducted by the same member of the research group which was considered as a way of improving the reliability in the comparison of the data. Interviews with the midwives were carried out mainly during their working hours, which may have influenced the total time spent in the interview. The place was carefully selected to ensure privacy. Saturation, which means that new aspect did not emerged (Polit & Beck 2006), became apparent after 16 interviews with the mothers (I), 18 interviews with the midwives (II) and after 3 focus- group interviews with the researchers (III). After the interviews had been transcribed, the written texts were compared with the original interview material to ensure that the transcription had been accurate. Although the material was analysed by one researcher, the multidisciplinary research group discussed the results at different stages of the analysis, which can be called investigator triangulation. The research group also worked together in reviewing the conceptualisation process and the concepts to be selected (for more discussion on triangulation see e.g. Polit & Beck 2006, Tong et al. 2007). Although the findings do not represent the views of all stakeholders in tissue research, the saturation of opinions with this the number of interviewees gives confidence that the results are reliable. This implicates that the results of this study can be utilised not only in Finnish placental perfusion studies, but also in general in studies requiring recruitment and informed consent procedures.

The focus group interview is a method where participants are encouraged to communicate with each other, ask questions and comment on each others' experiences and points of view (Kitzinger 1994, 1995, Barbour 2010). This method was chosen as a way to obtain a consensus about ethical aspects in perfusion studies and also to provide the scientists involved with a possibility to gain new perspectives. The purpose was not to gather individual comments, these were handled in the data analysis. On the contrary, the aim was to formulate a collective understanding about the topic. The language used in the focus-group interviews was English but this was not, of course, the native language of all participants. However, the participants were scientists and used to using English as a scientific language (see e.g. Barbour 2010). In the study III, two methods were used, focus-group interview and a questionnaire, both of which were very useful for the objective of obtaining a deeper understanding of the views of the researchers about ethical aspects. This made it possible produce information in a comprehensive manner, which was considered to strengthen this study. Furthermore, the results gained by both methods complemented each other. The analyses were done with the NVivo programme which proved suitable for this kind of study. When comparing NVivo analysis with the manual analysis used in study 1, it seems that the NVivo technique is not only more systematic but also more focused (see Bergin 2011).

Research involving documents is increasing (Al-Qadire et al. 2010, Prior 2010), and thematic analysis is an appropriate method for working with this kind of material (Prior 2010). In order to analyze the validity of documents, the analysis must consider the contents of the documents. In the statements of the ethics studied here (IV) the contents varied from a few sentences to long deliberations. Thematic content analysis was considered as the best method because of the variation in the length of the documents as recommended by Prior (2010). Thematic content analysis also makes it possible to use quantitative methods (Sandelowski 2001, Sandelowski et al. 2007). The topics of the statements about the ethics of research also were formulated according the instructions by the ethics committee. Such detailed instructions are commonly used and can lead to a certain type of text in the statements as also pointed out by Prior (2010), and this must be remembered, when drawing conclusions. A typical example is the concept of voluntariness which was used as a word without further explanation. On the other hand, when scientists had an opportunity to write a "Free statement," the content was less comprehensive than those that were written according to the instructions. In this case structured format may have lead the

scientists to just answering the requiring points and not challenge scientist to deeper consideration about ethical aspects in their research.

7 Summary and conclusions

1. The results of this study indicate that stakeholders, i.e. donors, recruiters and researchers, do not perceive any ethical problems or risks related to the scientific use of anonymized human placenta for pharmacokinetic studies involving placental perfusion. All stakeholders considered scientific research using human tissue as important, especially if the research benefits the society as a whole. It was notable that all stakeholders in perfusion studies have similar views about most of the themes used in this study.

2. The success of the research on human tissue requires fluent collaboration between different stakeholders. Both the studied nurses and mothers expressed that the decision process towards informed consent should be a dialogue between the stakeholders to ensure true informed consent from the participants. Based on results of this study and earlier literature it is clear that the informed consent process is challenging in the clinical setting. Thus, it is imperative to determine the factors influencing in the recruitment and informed consent process. Results also indicate that this is not possible without taking on account of the management and research governance. Therefore more research is needed concerning tissue research and the process of informed consent as well as on the stakeholders involved that process, also from the point of view of management and research governance.

3. Based on the opinions of the researchers in placental perfusion studies, the recruiting nurses or other persons should be part of the research team to ensure that the participants receive accurate information. Nurses pointed out that, more education about the methods and aims of the projects should be provided to them when they are involved as recruiters. This was also supported by the researchers. Nurses have an important role in recruiting patients for scientific research and therefore more research is needed to clarify further their opinions.

4. According to the stakeholders of tissue research societal meaning of tissue research is multidimensional and includes e.g. the significance of scientific knowledge, image of science and aspects of research ethics. Active communication was regarded as essential and according to all stakeholders should include both the general public and the scientific community. The scientist pointed out that Finland is already a multicultural country and global collaboration is increasing. Therefore, future studies should focus also on the cultural aspects of biomedical ethics.

5. The results of this study showed that ethical statements of the scientists were quite shallow. The significance of ethical questions in the use of human tissue for research purposes will probably increase in the future, especially when more biobanks of human tissues are established. In order to obtain more generalized information, it is essential to review other ethical statements and study protocols. In addition, it would be important to gather the views of participants about tissue research in general, for example about the commercial use of human tissues. Additionally, continuing education about research ethics is needed.

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Arja Halkoaho

Ethical Aspects of Human Tissue Research

Views of the Stakeholders

Ethics is a central aspect in scientific research and it is more than law. The aim of this study was to describe the ethical aspects of human tissue research and to learn how the stakeholders in research involving human tissues perceive their participation and how the protection of their rights is guaranteed by current ethical practise. Research using human tissue may increase in the future e.g. when large biobanks are established. Views of different stakeholders in research could contribute to research ethics by both improving the ethical conduct of recruitment and increasing participation.

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