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Legal and ethical aspects associated with nanomedicine in patient care.

A literature review

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ERASMUS UNIVERSITY ROTTERDAM, IBMG 2013-2014

Abstract (English)

This research has been done in order to gain a better understanding of the way that legal and ethical aspects are associated with nanomedicine in patient care. The field of nanomedicine is one that is very unique in comparison to other fields of research. The field of nanomedicine still has many uncertainties and unknown potential (long term) effects. This thesis has been written in order to create an information platform on the subject that is better accessible for both the representatives of the legal field as well as the representatives of the medical field. The problem this thesis tries to address is the giant gap that exist between the different fields of expertise in regard to the subject of nanomedicine in patient care. By reviewing the available literature on the subject of nanomedicine written in the viewpoint of the medical specialists, the legal specialist and the ethical specialist, this thesis has tried to unify these three different viewpoints. When these three viewpoints can be unified, than the problem of the information gap will become less substantial.

During this research a large amount of articles, reports and opinions of various experts, researchers and administrations has been gathered and reviewed for their scientific value and information. This information has been processed by means of a set of research questions which were used to create a framework for the available information. This framework of sub-questions was meant to provide an answer to the main research question, which was what legal and ethical aspects are associated with nanomedicine in patient care?

The results of this research showed that there is a great number of legal as well as ethical aspects that are associated with nanomedicine. Most aspects are associated with the potential of unforeseen risks and side-effects. These aspects include the problem of the non-existence of a specific set of rules and regulations for the field of nanomedicine and the ethical dilemmas that these potential uncertainties may affect.

From challenges regarding the dignity of individuals to the potential of legal loopholes because of the absence of a regulatory framework. These are all completely different in nature, but they all have one thing I common and that is that there is still a large amount of uncertainty on the subject. Whether it's about the potentials risks of nanomedicine, the way that people's individual rights and privacy will be affected or how to incorporate nanomedicine into a legal framework. Much is still unclear and further studies and research are needed if nanomedicine is ever to be implemented into modern day medicine

Samenvatting (Dutch)

Dit onderzoek is gedaan met de reden om een beter begrip van de manier waarop juridische en ethische aspecten worden geassocieerd met nanogeneeskunde in de patiëntenzorg te krijgen. Het veld van de nanogeneeskunde is er een die zeer uniek is in vergelijking met andere onderzoeksvelden. Het veld van de nanogeneeskunde heeft nog steeds vele vormen van onzekerheid en onbekende potentiële (lange termijn) effecten. Deze scriptie is geschreven om een informatieplatform voor het onderwerp te creëren dat beter toegankelijk is voor zowel de vertegenwoordigers van het juridisch gebied, alsmede de vertegenwoordigers van de medische sector. Het probleem dat deze scriptie probeert te adresseren is de gigantische kloof die er tussen de verschillende vakgebieden met betrekking tot het onderwerp van de nanogeneeskunde in de patiëntenzorg is. Door de verwerking van de beschikbare literatuur over het onderwerp nanogeneeskunde geschreven in het standpunten van de medisch specialist, de juridische specialist en de ethische specialist, heeft deze scriptie als doel om deze drie verschillende standpunten te verenigen. Wanneer deze drie standpunten kunnen worden verenigd, dan zal het probleem van het gebrek aan informatie minder groot wordt.

Tijdens dit onderzoek is een grote hoeveelheid artikelen, rapporten en adviezen van verschillende deskundigen, onderzoekers en organisaties verzameld en beoordeeld op hun wetenschappelijke waarde en informatie. Deze gegevens zijn verwerkt door middel van een set van onderzoeksvragen die werden gebruikt om een kader voor de beschikbare informatie te creëren. Dit kader van deelvragen was bedoeld om een antwoord te creëren op de centrale onderzoeksvraag, welke juridische en ethische aspecten worden geassocieerd met nanogeneeskunde in de patiëntenzorg?

Uit de resultaten van dit onderzoek bleek dat er een groot aantal juridische en ethische aspecten is dat verbonden is met nanogeneeskunde. De meeste houden verband met de mogelijkheid van onvoorziene risico’s en bijwerkingen. Deze aspecten omvatten het probleem van het niet-bestaan van een specifieke set van regels en voorschriften voor het gebied van de nanogeneeskunde en de ethische dilemma's die deze potentiële onzekerheden kunnen beïnvloeden.

Van uitdagingen met betrekking tot de waardigheid van het individu tot het potentieel van mazen in de wetgeving als gevolg van het ontbreken van een regelgevend kader. Deze zijn allemaal heel verschillend van aard, maar ze hebben allemaal een ding in gemeen en dat is dat er nog steeds een grote mate van onzekerheid over het onderwerp bestaat. Of het nu gaat over de mogelijke risico's van de nanogeneeskunde, de manier waarop individuele rechten van mensen en hun privacy zal worden beïnvloed of hoe nanogeneeskunde op te nemen is in een juridisch kader. Veel is nog onduidelijk en verdere studies en onderzoek zijn nodig als de nanogeneeskunde ooit in de hedendaagse geneeskunde te implementeren moet zijn.

Content

Foreword

This thesis is the final challenge I had to overcome before achieving my bachelor of science. But it signifies much more than that, for me it is the first expression of my own research and the culmination of everything I have learned over the past three years. For those of you who will read it or those of you that find it useful, my thanks goes out to you. As you will most undoubtedly find out the world of nanomedicine is much more complex and intricate than simply the different kinds of research. It consists of much more than scientists and medical professionals, but also of legal practitioners, ethical scholars and economic and political professionals. My hope for you, the reader, is that you will be able to better understand the different points of view and interests that these faction have, but also that they need to work together in order to be successful. It has been quite difficult at times to continue working when you whole life seems to come crashing down around you, but I think I managed in the end. My thanks goes out to those who supported me and gave me comfort when I needed it the most. But for now, enjoy your reading

Introduction

It has been said that one of the worst things you can and most of the times will endure in this life is to bury your parents. Despite that it is the natural order of things, it is still something that none of us would wish upon another. In today's society most children don't have to bury their parents until they are very old and have lived a full and meaningful life. A few years ago however I myself came very close to having to bury one of my parents. The cause for this was not old age, but an affliction that brought my father very close to an early grave. My father had been diagnosed with cancer. The moment that my father called me and told me the news is something I will never forget till the day that I die. I still remember the first thing I asked him, after quite an awkward moment of silence. "How much time do they say you have left?" My father said they didn't know yet, because they weren't sure what type of cancer it was. The preliminary results showed a type of cancer known as Hodgkin syndrome, a type of cancer that spreads itself through the vessels of the lymphatic system (Armitage 2010). Hodgkin Syndrome is a very aggressive type of cancer which has a relatively high survival rate, around 83%, but is nevertheless still a very dangerous and taxing disease. The thought of my father being subjected to radiotherapy and chemotherapy was not one I greatly enjoyed. In order to find out what type of cancer it really was they had to perform an operation, to see the cancerous growth up close and determine whether it was malign of benign. The results of this operation showed that the growth was not located inside of the lymphatic system but beside it and its cells were benign. The diagnoses was revised, Non-Hodgkin Syndrome with a low classification, meaning non aggressive (Maeda et al. 2009). This was somewhat of a relief amongst our family, but the amount of stress everybody was in between the first diagnosis and the final diagnosis was unimaginable. The fact that they had to perform an operation in order to actually verify the diagnosis is something that to me seems quite outdated. Not only because it's a very taxing procedure all on its own, but also because it takes a lot of time. Time that could otherwise be used to combat the disease.

During that time period I was looking into alternative methods to treat my father's disease and came across an experimental technique which used microscopic particles inside of the body to locate and sometimes even destroy cancerous growths. Needless to say this peaked my interest greatly and I began to look into other procedures that used a similar approach. These new and experimental procedures are capable of creating a detailed picture of cancerous growths, but can also be used to deliver medicine intravenously at the correct location in the body. In some of the available literature it is described as the most promising step in healthcare since the invention of antibiotics (McHale 2009). I'm of course talking about the field of nanomedicine. At that time the use of nanomedicine in order to better treat my father seemed like the perfect solution to me. When I asked my father's physician about

the possibility of these procedures he said that it would not be possible to use these. Not only because they were not allowed in general practice, but also because they were still in the experimental stages. “These experimental procedures do show promising results, but they are still not recommended for general practice.” These were the words my father’s physician used to describe the application of nanomedicine. At the time I was furious at the man for not even wanting to try and he said that he didn’t have a choice in the matter because it wouldn’t be ethical. After a few weeks I realized that my dad’s physician was actually right. Was it okay of me to want my father to be treated by an experimental procedure, because his chances of survival would be marginally better? In the hope of finding an answer to that question for myself I started to explore the possibilities of nanomedicine and came across a rather idealistic description of nanomedicine.

“Nanomedicine aims at ensuring the comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures, ultimately to achieve medical benefit (Nature Materials 2006).”

What this definition actually implies is that nanomedicine should be used for the medical benefit of all human biological systems, using technologies on a molecular level. The amount of improvements and chances that this represents are phenomenal, but it also has a downside. When you operate on a molecular level, how can you safely assume that procedures wont’s have a larger scale effect and is it not also possible to use the same technology in order to harm certain human biological systems? I can even imagine there would be some religious objections to these forms of medicine and treatment, because they “mess around” with the building blocks of human existence. And apart from the ethical objections, is it even allowed? Are there no laws that prevent this kind of research of try to guide it onto safer tracks? The main questions that concerned me before I began with an in depth research into the subject was: Is it responsible to always do everything we can do, or should we focus on what we should do and are allowed to do? In order to find an answer to some of these questions I decided to take up this thesis. In the hopes of creating a more consistent and understandable vision of nanomedicine, whilst taking into account the subjects of health law and ethics.

In order to understand the connection between nanomedicine, health law and ethics it is first necessary to properly define the terms and the way in which they will be used during the research. Secondly the terminology has to be conceptualised properly, this means using the appropriate research questions that will take into account all three terms. Apart from that the answers to the research questions also have to be logical and have to be understandable for

both legal representatives and medical professionals. The answers to said research questions will be the core of this thesis and will synthesise the information of the available literature in order to achieve a more fitting answer. In conclusion I will present an answer to the main research question and discuss the shortcomings of this thesis.

But what is the relevance of nanomedicine, apart from the aforementioned benefits in the medical field (Mchale 2009). Almost everybody will have seen it in the papers, the online headlines, the news or even talk shows. The size and cost of the healthcare system in the Netherlands is growing exponentially (VWS 2012). This means that it will be increasingly difficult for healthcare organisations to offer both an acceptable price as well as the highest standard of healthcare. This is not only due to the growing population or the ever increasing percentage of seniors, but also because the quality of care, and therefore the standard of healthcare, is constantly improving (Horst et al. 2011). The question that is rightly put forward in the rapport of the ministry of public health, welfare and sports (VWS) (2012) asks us how much extra we are willing to pay for our healthcare. This increase in health expenditures has a great societal impact, because it affects everyone. Both the lower and the higher social classes will see an increase in their expenses with an expected percentage of income being spent on healthcare of approximately 31% by 2040 (Horst et al. 2011). Finding new and improved medical procedures is still at the top of the list for most researchers, but what about the cost of these procedures? In order to sustain our healthcare system and to keep providing the highest possible quality of healthcare with the available amount of funding, it will be necessary to look for new and innovative forms of medicine. The usage of nanomedicine would be one of those innovative techniques.

The goal of this thesis is to find out whether such a new form of medicine will be ethically correct to use and whether or not it's legal. Finding a compromise or common ground between these two approaches to nanomedicine will create a stronger foundation for further research into the subject. At the moment nanomedicine is still in its early stages and most of the research on the subjects focuses either on the ethics that are involved or the legal barriers and possibilities. Nanomedicine is one of the more tricky subjects when it comes down to the actual implementation, because the nature of its procedures is such that actually doing everything that can be done with it, may not be everything that should be done with it. By this I mean that some procedures and possibilities of nanomedicine might be legal to do, but are they also ethical or vice versa. Take for example this question: Is it acceptable to perform a procedure that isn't medically warranted, for reasons of defensive medicine? If the answer to this question would be no, than that could mean that a professional will not use an unwarranted technique such as nanomedicine even though it could potentially safe a life. If the law states that unwarranted procedures are not allowed, but it could potentially save a

life, then you are faced with an ethical dilemma. In such cases the line between what is “right” and what is “wrong” is extremely hard to discern. I would even go as far as to say that it is practically non-existent. Navigating through the sometimes small gap between ethics and legal aspects can therefore be extremely hard. My hope is that for the field of nanomedicine and its future uses and implementation in patient care, this thesis will function as a sort of roadmap. That will allow representatives and researchers of both the legal and medical profession to find a common ground on which they can work together to further improve the healthcare system. Improvement and maybe even redevelopment of this system is needed, because in the future the current system will no longer be sustainable and will become too expensive (VWS 2012). Innovation of our healthcare system is necessary, but the way that innovation is achieved and formed should also be monitored carefully. For what good is it when you can cure every disease imaginable, but the treatment is only accessible to a few, while the rest is stuck with an outdated and ineffective method. Such is the case with nanomedicine, because it can offer a range of possibilities and improvements, but also has to be monitored and controlled. Not just to make sure it stays within the confines of the law, but also to make sure that it develops in an ethically correct way. Therefore the fields of ethics and health law are intertwined concerning the subject of nanomedicine. In the coming chapters nanomedicine and health law will be examined, nanomedicine and ethics and the discrepancies that exist between these two subjects on the matter of nanomedicine.

Research questions and theoretical background.

Presenting the information about nanomedicine and the connection it has with health law and ethics correctly is difficult to achieve without first understanding the respective subjects and there dependency. In order to achieve this, the upcoming chapters will be divided using different research questions. Apart from that the general direction of the research will be determined by a primary research question, pertaining to all three fields. This research question will be:

"What are the current legal and ethical aspects associated with nanomedicine in patient care?"

The aim of this research question will be to create an information platform which can later be used by others who are researching the same subject. The choice to look at the legal and ethical aspects associated with nanomedicine was made because it is one of the more crucial fields necessary for implementing a new technology, in my opinion. Because even if something is possible or can be done, we should, as a species, always ask ourselves whether we should. In my opinion a conscience and a sense of ethics is what makes us human and separates us from other species of animals. In order to facilitate the research into this matter a number of sub-questions have also been set up. These sub-questions will help to better understand and handle the information retrieved from numerous sources of literature. These sub-questions are:

- What is nanomedicine and what are some of the reported risks?
- Which benefits can be derived from the use of nanomedicine?
- How should nanomedicine be conceptualized in health law and ethics?
- What are the opinions expressed by expert stakeholders concerning the ethics debate of nanomedicine?
- In what way are there discrepancies between health law and ethics, concerning the field of nanomedicine

The first sub-questions are mostly definition questions which will serve to process the information on nanomedicine and some of the risks and benefits that come with the technology. The conceptualised definition of nanomedicine will be necessary to understand the connection between these possible risks and benefits. The risks and benefits that will be researched are only those that are directly involved with patient care. The third sub-question will be about conceptualising the term nanomedicine so that in can be applied to the fields of health law and ethics. This is necessary to determine the way nanomedicine relates to ethics and health law. This way its position within the current laws can be determined and the ethical controversies that it might produce. To create a more in depth account of these

ethical controversies, the opinions of expert stakeholders and researchers will also be incorporated. This will create a scientific approach to the ethics debate, concerning nanomedicine, so that by congruence of several opinions it may become more objective and measurable. The final sub-question will function to highlight the differences and possible difficulties that the unification of ethics and law may pose on the subject of nanomedicine. This question will function to illustrate the sometimes very complicated reality and the way that it can house certain discrepancies, usually when ethics are involved. Using these five sub questions I hope to find a nuanced and complete image of the way that nanomedicine, patient care and the respective Dutch laws, European and international treaties that apply to these areas, coincide with one another.

Theoretical background

As mentioned before, the field of nanomedicine is quite diverse and is comprised of a multitude of subjects (Glenn & Boyce 2012). It encompasses everything from the use of personalized medicine down to the more experimental use of nanotechnology to repair damaged cells. With the correct amount of time and effort someone will be able to one day cure cancer and any other type of disease that plagues mankind, but the possibilities extend even further than that. This is of course all theoretical, but even things such as selective mutation, to expand human life spans and boost immune systems, and biomechanical enhancement, augmentation of biomechanical limbs to create stronger humans, are possible using nanotechnology en nanomedicine. For now however, the applications of this wondrous technology are still mostly in developmental stages and some are still only speculation (Glenn & Boyce 2012).

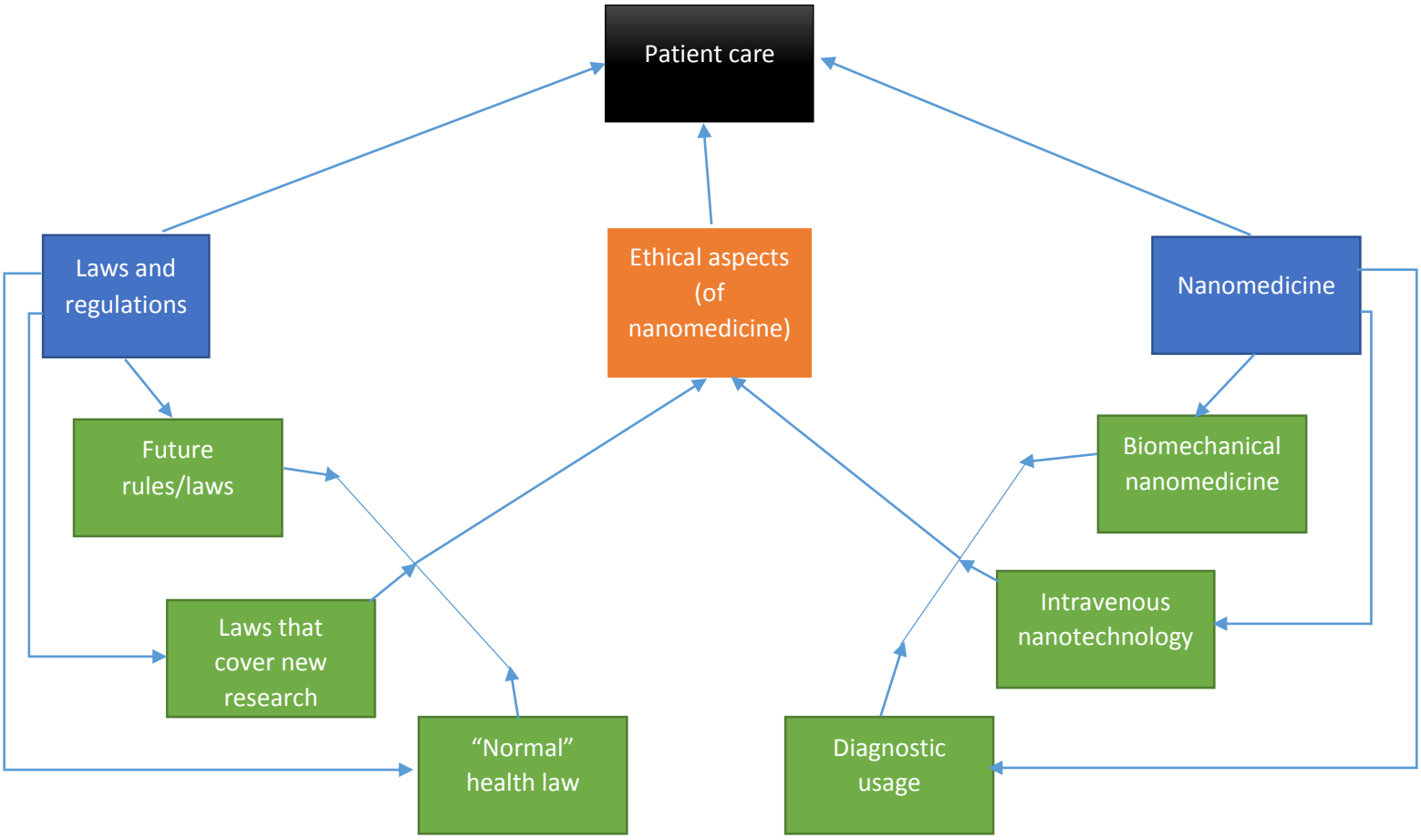
But this great diversity also makes it hard to review one specific type of procedure, because most of the research encompasses a few of the available research fields at once. Meaning not only the specific field of nanomedicine, but also fields such as: bioengineering, robotics, virology and even ecology (Spagnolo & Daloiso 2009). Because of this diversity I have chosen to only look at the types of nanomedicine that have already been cleared for usage in patient care or are soon to be. These include usages such as: nano tattoos (Bennet & Naranja 2013), drug delivery systems (Chowdhury 2010) and imaging technologies (Hock et al 2012). These different applications all use some form of nanomedicine and will be explained more thoroughly later on. I will however not be explaining all of these procedures in detail, for that is not the aim of this research. As mentioned before the aim is to explain the connection between the ethical and legal aspects associated with the use of nanomedicine in patient care and create an information platform which that is accessible to both the medical and legal field professionals. The definition of nanomedicine in this thesis will therefore be based on the definitions provided by the authors that have already explored the

subject. Such as Spagnolo & Daloiso (2009), who have made a partial overview of the ethics involved with nanomedicine and Mchale (2009), who gives an insight into the regulatory challenges that implementing nanomedicine in the EU may bring. Using the views, opinions and facts supplied by several authors and combining them with my own insights and findings, I aim to create a better overview of the subject.

In order to create a better oversight for this thesis I have constructed a conceptual web (figure 1), which is designed to highlight the connections between the separate fields and the underlying implications of these connections. As well as highlighting these connections, the conceptual web will also function to give a definition and explanation of the separate factors that play a role in the research of this thesis. Whilst giving a complete overview of the subject at hand.

Conceptual web

Figure 1conceptual map showing the connections between nanomedicine, law and patient care



The connections explained

- Laws and regulations are divided into three different sections: future rules/laws, laws that cover new research and the "normal" health laws.

- Nanomedicine has been divided into three basic areas of research: biomechanical nanomedicine, intravenous nanotechnology and diagnostic usage.
- Both the three areas of law and the three research areas of nanomedicine are related to the ethical aspects concerned with the usage of nanomedicine and patient care
- The ethical aspects are always present in the field of law and the field of medicine, the combination of these two fields however creates an entire new set of possible ethical aspects.
- Patient care is the central end goal and is therefore dependent upon and influenced by all the other aspects. It is already subject to laws and regulations. Nanomedicine, despite being in the developmental stages, is already being used in several procedures and so already influences patient care. This influence will continue to grow as the research progresses. The ethical aspects created by the variables law and nanomedicine will add to the already present effect of ethics on patient care. The manner in which these ethical aspects will be dealt with will determine the progression rate of nanomedicine research. Apart from that it will also have to be taken into account that if the benefits and possibilities start to outweigh the dangers and ethical problems, whether that is the correct path to follow or that this has to be restricted.

Definition of concepts

Laws and Regulations: the whole of the legal rules and regulations concerned with healthcare and the field of medicine.

New rules and laws: the new legal aspects and adjunctives that are made in order to encompass new fields of technologies, such as nanomedicine.

Laws that cover new research: these are existing laws that have already been created in order to encompass new medical technologies and advancements in medicine.

Normal health Law: the current laws and rules concerning the healthcare sector

Nanomedicine: The research field that concerns itself with the medical application of nanotechnology. Ranging from nano imaging tot molecular nanotechnology.

Biomechanical nanomedicine: the most advanced form of nanomedicine, combining both the biological side of the human body and the technological side of the research field. Consider things like nanites that have the capability to repair damaged skin tissue.

Intravenous Nanotechnology: The most promising form of Nanomedicine. With the intravenous technologies the medical community will be able to precisely deliver and manage for example drug delivery, using nano-lipids.

Diagnostic usage: this is the most researched and common form of nanotechnology in patient care, which is already being used on a more regular basis. Think of things like imaging technologies to create an image of the spread of a tumour.

Research design

The design of this thesis will be neither quantitative nor qualitative. Instead I have chosen for a literature review. The reason for this is that the subject of nanomedicine and the ethical and legal aspects associated with it is still very new. Because of this the amount of information on the subject is not in abundance and the information that is available never encompasses the entire subject. In order to unify these bits of information and to create a more complete source of information on the subject an exploratory literature review is the most logical choice. This form of research will help me achieve the main goal of this thesis, namely the creation of a more complete information platform for both the medical and the legal field, on the subject of nanomedicine, and apart from that it will help me to find an answer to my main research question. To achieve this I will be using a literature review approach that is called a systematic review, its main purpose is to identify and appraise all relevant information necessary to answer a research question (Levy & Ellis 2006). During a literature review it is important to take into account that you are using the findings and results of other authors. So it is always important to give acknowledgement to authors and their work, not only because it is constituted as fraud if you don't, but also because it's the "ethically correct" thing to do.

During this research I will have to appraise and process a lot of articles and results. In order to do this as objectively and professionally as possible I will be using a three step procedure (figure 2) which is based on Blooms Taxonomy (Levy & Ellis 2006). These three steps consist of the input, processing and output. The processing step is the review itself, in which I will follow the six steps of Bloom's taxonomy to process literature correctly.

1. Know the literature (knowledge)
2. Comprehending the Literature (understanding)
3. Apply (use in other ways)
4. Analyse (break information into parts)
5. Synthesize (compile information in a new pattern)
6. Evaluate (construct a judgement)

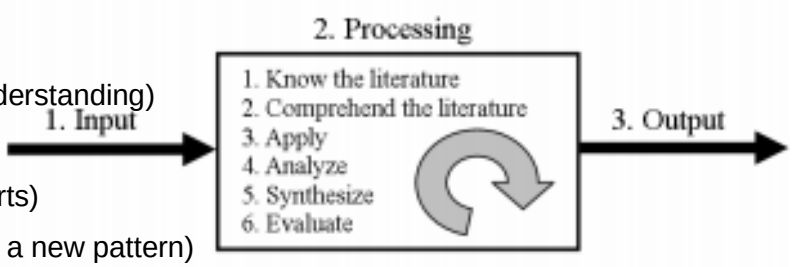


Figure 2 The three steps used in a review using Bloom's Taxonomy (Kratwohl 2002).

The first step of the process is knowing the literature, because knowing is the first step to understanding. This knowledge of the literature however is not enough. Knowing the literature only means that you are aware what literature there is and know what can be found within the available literature (Levy & Ellis 2006). Apart from knowing the information that is available, I will also have to comprehend the information that is presented. Comprehension of the given information means that I will not only be able to reproduce the information, but also to explain it to others and on paper. Knowledge without comprehension mostly leads to

a misinterpretation of the information and is therefore undesirable (Krathwohl 2002). Once I comprehend the information in the literature I will be able to apply it. Applying the acquired knowledge means putting it in different context and form, thus using the knowledge to come up with ways to solve a new and unfamiliar problem through didactic reasoning. Apart from applying the information it is also mandatory to analyse the information that is at your disposal (Krathwohl 2002). Analysing the given information means breaking it up into separate “bits”, bite sized chunks of information. When your available information is broken up into separate components it is much easier to use takes on the form of a very easily overview structure. Because the information has been split into smaller chunks it can be regrouped into new structures and combination, making it possible to create and construct new information with what you already have. This synthesising is a different form of didactic reasoning, but more thorough (Levy & Ellis 2006). After having gone through these steps it is crucial to evaluate what you have done. The evaluation will help me filter through the information, thus making it able to segregate usable and unusable bits of knowledge.

Using these steps in the review process is necessary to create an output that uses the reviewed literature to build upon existing facts and ads to the available information pool. By following these steps I will be able to construct an effective systematic review. In order to preserve the validity of this research I will be using a logical construction of facts, results and arguments in which the conclusion will be logically entailed by its premises. This is a basic prerequisite for any kind of research, but within a literature review it is one of the most important things of all (Johnson 2000). Reliability is very difficult to achieve in a literature review, mostly because not everyone comes to the same conclusions with the same information. Just as in the literature itself, there are many different opinions and points of view. The processing of information is always subject to the subjectivity of the processor. So the conclusion I will reach in this research may differ from that of another, who is given the same information (Johnson 2000). It is however my aim to present my findings in such a logical way that others will reach the same conclusion as me, therefore solidifying the reliability of this thesis. The next few chapters will therefore be devoted to reporting my findings and opinions on the five research questions that have been introduced earlier. The answer to these questions will be constructed using the basic principles of Bloom’s taxonomy and will function to answer the main research question of this thesis in the conclusion.

What is nanomedicine and what are some of the reported risks?

Definition

In the previous chapters the term nanomedicine has been introduced. You have already seen a number of examples of what this term can entail. These include usages such as: nanotattoos (Bennet & Naranja 2013), drug delivery systems (Chowdhury 2010) and advanced imaging technologies (Hock et al 2012). Each of these applications is very different from the other, not only because they include different fields of research but also because they have different goals. So is it possible to say that there is a general definition that encompasses all the different fields and goals that nanomedicine is related to. Let's assume it isn't and work from there. Take for example the following definitions of the term nanomedicine:

> *"Nanomedicine aims at ensuring the comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures, ultimately to achieve medical benefit (Nature Materials 2006)."*

> *"Nanomedicine is very broadly defined as a technology that uses molecular tools, nanotechnology, and knowledge of the human body for medical diagnosis and treatment (Wagner et al 2006)."*

> *"An offshoot of nanotechnology, which refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve (NIH 2006)."*

As you can see there is a difference between each of the definitions on the subject. All three of the definitions do have in common that nanomedicine is a form of nanotechnology that functions on a molecular scale for a medical purposes, but this is where the similarities end. The first definition is that put forward by the European Science Foundation (ESF) and sees nanomedicine as an independent form of medicine that will ultimately be used for medical benefit. Whereas the third definition is that put forward by the American National institutes of Health (NIH). According to this definition nanomedicine is not an independent field of medicine, let alone an independent research field. The differences between the views of the ESF and the NIH is quite substantial and can cause differences in the way that nanomedicine will develop itself. Apart from that the way nanomedicine is defined can influence the way that nanomedicine is viewed by the public and therefore whether it will be deemed viable enough to implement into normal medical procedures. (Wagner et al 2006).

When looking at these separate definitions of nanomedicine it is safe to say that there is not a single all-encompassing definition of the subject. Mostly because there is not a general international definition of the term, but also because the emphasis on each definition has

been made from a different point of view regarding nanomedicine. Even within the different points of view there is no one definition that is absolute. Take for example the definition of nanomedicine by the NIH (2006). According to them nanomedicine is an offshoot of the field of nanotechnology. But the questions that comes to mind at this point is, what is nanotechnology exactly? Even on the subject of nanotechnology however there is still quite a lot of debate going on to determine what qualifies as nanotech and what doesn't (Khushf & Siegel 2012). Although the discussion is mainly about the size that the technology or nanostructure should have, between 1-300 nm or between 1-100 nm (1 billionth of a meter), it still hinders the uniformity of a definition (Khushf & Siegel 2012). So to say that something belongs to the field of nanotechnology or even the field of nanomedicine is not always that easy. Because what falls into the category according to one of the definitions may be excluded by another. So in order to give a general definition of the term nanomedicine, the experts will first have to decide what exactly it is. Whether it's a field of research all on its own or an offshoot of the field of nanotechnology and whether or not something is small enough to be called nanotechnology is determined by the point of view someone has regarding the subject and until a consensus is reached between the majority of experts and stake-holders, there will be no general definition of nanomedicine. So for now the term nanomedicine is only broadly classified as a form of nanotechnology that is used on a molecular scale for medical purposes.

Despite there not being a general definition, there are numerous applications and usages of nanomedicine that have been unanimously acknowledged as such (Wagner et al 2006). These usages range from drug delivery to imaging enhancers and even artificial enzymes. These three applications are just the metaphorical tip of the iceberg when it comes to the uses and possibilities (Table 1) that the field of nanomedicine can offer. The field of nanomedicine may not have a general definition in order to say what it is, but the independent parts and medical technologies can be explained to give a better understanding of the overall subject.

- Immunoisolation: one of the simplest approaches to nanomedicine, a surface perforated with tiny holes, nanopores. This can be used to encapsulate foreign elements inside the human body, therefore making it possible for tiny molecules such as insulin, oxygen and water to pass through. The holes in this surface are however not big enough to let antibody's pass, therefore making the foreign material undetectable for the host bodies' antibodies (Freitas 2005).

Table 1 a list of the different uses of nanomedicine (Freitas 2005)

Raw nanomaterials	**Cell simulations and cell diagnostics**	**Biological research**
Nanoparticle coatings	Cell chips	Nanobiology
Nanocrystalline materials	Cell simulators	Nanoscience in life sciences
Nanostructured materials	**DNA manipulation, sequencing, diagnostics**	**Drug delivery**
Cyclic peptides	Genetic testing	Drug discovery
Dendrimers	DNA microarrays	Biopharmaceutics
Detoxification agents	Ultrafast DNA sequencing	Drug delivery
Fullerenes	DNA manipulation and control	Drug encapsulation
Functional drug carriers		Smart drugs
MRI scanning (nanoparticles)	**Tools and diagnostics**	
Nanobarcodes	Bacterial detection systems	**Molecular medicine**
Nanoemulsions	Biochips	Genetic therapy
Nanofibers	Biomolecular imaging	Pharmacogenomics
Nanoparticles	Biosensors and biodetection	
Nanoshells	Diagnostic and defense applications	**Artificial enzymes and enzyme control**
Carbon nanotubes	Endoscopic robots and microscopes	Enzyme manipulation and control
Noncarbon nanotubes	Fullerene-based sensors	
Quantum dots	Imaging (cellular, etc.)	**Nanotherapeutics**
	Lab on a chip	Antibacterial and antiviral nanoparticles
Artificial binding sites	Monitoring	Fullerene-based pharmaceuticals
Artificial antibodies	Nanosensors	Photodynamic therapy
Artificial ezymes	Point of care diagnostics	Radiopharmaceuticals
Artificial receptors	Protein microarrays	
Molecularly imprinted polymers	Scanning probe microscopy	**Synthetic biology and early nanodevices**
		Dynamic nanoplatform "nanosome"
Control of surfaces	**Intracellular devices**	Tecto-dendrimers
Artificial surfaces—adhesive	Intracellular assay	Artificial cells and liposomes
Artificial surfaces—nonadhesive	Intracellular biocomputers	Polymeric micelles and polymersomes
Artificial surfaces—regulated	Intracellular sensors/reporters	
Biocompatible surfaces	Implants inside cells	**Biotechnology and biorobotics**
Biofilm suppression		Biologic viral therapy
Engineered surfaces	**BioMEMS**	Virus-based hybrids
Pattern surfaces (contact guidance)	Implantable materials and devices	Stem cells and cloning
Thin-film coatings	Implanted bioMEMS, chips, and electrodes	Tissue engineering
	MEMS/Nanomaterials-based prosthetics	Artificial organs
	Sensory aids (artificial retina, etc.)	Nanobiotechnology
Nanopores	Microarrays	Biorobotics and biobots
Immunoisolation	Microcantilever-based sensors	
Molecular sieves and channels	Microfluidics	**Nanorobotics**
Nanofiltration membranes	Microneedles	DNA-based devices and nanorobots
Nanopores	Medical MEMS	Diamond-based nanorobots
Separations	MEMS surgical devices	Cell repair devices

- Nanoshells: the use of nanoparticles or liposomes bonded with medicine in order to improve the pharmacokinetic (ability to travel through the body) properties of a drug, making it more effective and faster (Wagner et al 2006).
- Microbivores: this can also be called a mechanical white blood cell. The function of this microscopic robot is the same as that of any other white blood cell. The difference however is that the microbivore is a kind of super white blood cell, because it is able to destroy much more pathogens than a normal white blood cell (Freitas 2005).
- Tectodendrimers: tree-shaped synthetic molecules that are shaped to be able to bond with others of the same kind, with different functions. These so called smart-molecules can be outfitted to recognize diseased cells, give a diagnosis of the disease state, delivers the correct drugs, report the location of the disease and report the outcome of the drug therapy (Freitas 2005).

- Radio-controlled biomolecules: these can also be called tiny gene factories. Their function is to make specific strands of DNA split and create different enzymes or hormones. These radio controlled biomolecules deliver therapeutic gene-manufacturing template to specific cell, turning them into automated auto-immunisation factories (Leary 2010).

These are just some examples of what the field of nanomedicine is capable of. When looking at these methods and procedures it is hard to imagine a downside to the field of nanomedicine. The reality however is that nothing can be further from the truth. The technologies and advancements behind all of these procedures are not all positive and sometimes can even be dangerous. As with all great things in life, the positive is always mixed in with the negative and the amount of risks and dangers that nanomedicine can represent is not to be taken lightly.

Reported Risks

The potential that the field of nanomedicine has far surpasses that of the risks that are associated with it (Oberdörster 2010), but without proper control and safety even the tiniest of faults can have far reaching consequences. Therefore it is necessary that research into the dangers and risks associated with the use of nanomedicine is undertaken proactively and that the potential risks are not played down in favor of the positive effects.

"With great power comes great responsibility."

-Voltaire-

With the field of nanomedicine the famous quote of Voltaire is as relevant as it has ever been. The powers and possibilities that nanomedicine and nanotechnology offer are quite substantial, but the dangers and risks are still not completely clear. In order to gain a better insight into the potential risks of nanomedicine it is first necessary to gain a better understanding of the way that nanoparticles interact with living cells, organisms and organs (De Jong & Borm 2008). For now there are already a few reported risks that are being researched, but the downside of this research is that it is impossible to say what the long term effects of the nanoparticles will be. The fact is that there is no way to say for certain what prolonged exposure to nanoparticles can cause to the human physiology. For now the research that is taking place is mostly aimed at discovering the tolerance dose, by administering a very high dose of nanoparticles to laboratory rodents over a short period of time (Oberdörster 2010). This is however one of the more easily identifiable risks that any new form of medicine has to be tested for. The nature of nanomedicine introduces an entire

new area of potential risks as opposed to the regular fields of medicine. That is because one of the distinctive characteristics of nanomedicine is also one of the greatest dangers it poses. The size of a nanoparticle is roughly between 1-500 nm, depending on the definition of nanoparticle you support. Because of its size a nanoparticle or capsule can travel to the most precise destination possible, because it can even pass through the blood brain barrier and the individual cell membranes (figure 3).

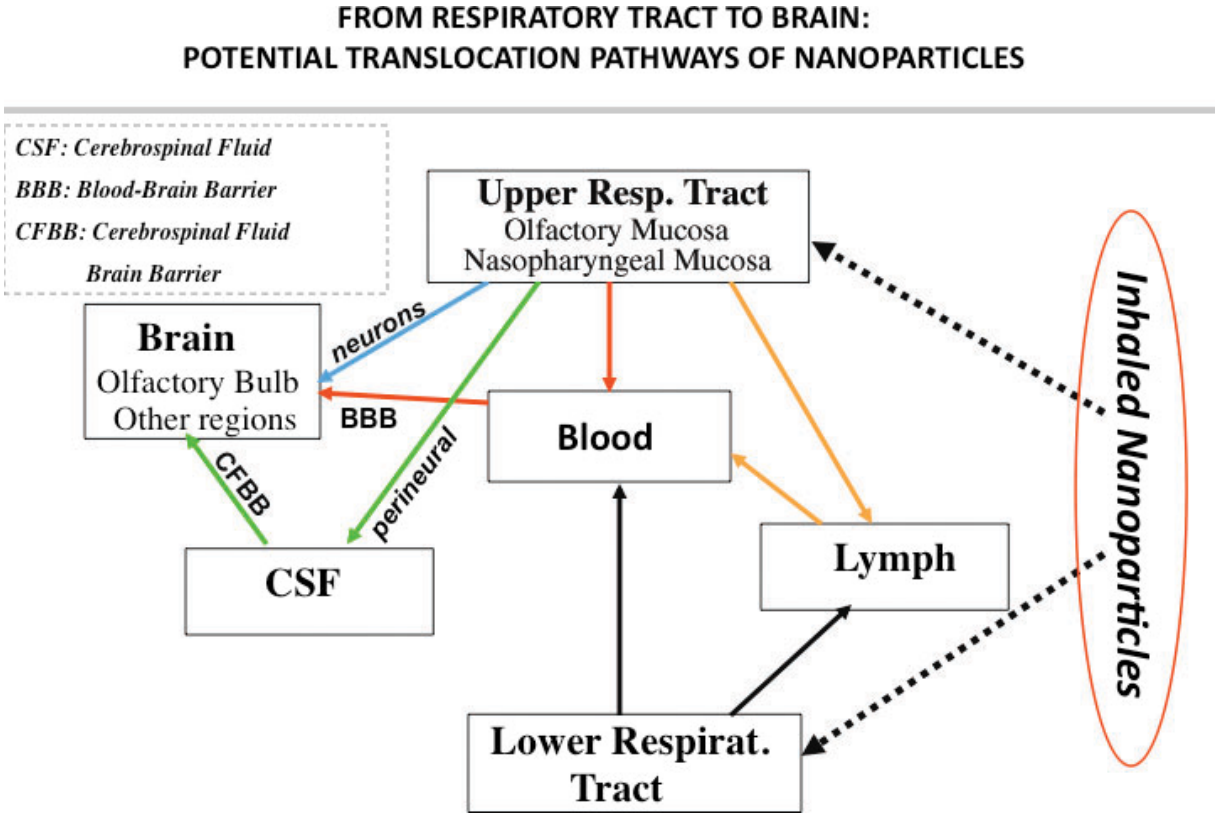


Figure 3 Potential spread of nanoparticles through inhalation (Oberdörster 2010).

This is also one of its biggest downsides, because when a particles this small is somewhere inside your body it can travel anywhere (De Jong & Borm 2008). Because the nanoparticle can get anywhere it can potentially interact with any number of cells and tissues. These cells and tissues are all exposed to the potential toxicity that these particles introduce into the system. The amount of toxicity and the amount of exposure to these particles depends solely on the way that the nanoparticles are constructed and designed, but as of yet there is no standard or blueprint (De Jong & Borm 2008). Therefore more thorough and more specific testing is necessary before further trials or even implementation in patient care can take place. At the moment however the research into nanomedicine is mostly centered on the potential benefits it can provide for the medical field and not on the potential side effects or physiological risks that it might entail (Linkov et al 2008). In order to circumvent these dangers and to achieve a successful development of future nanomedical devices and pharmaceuticals, an equilibrium in research between risk assessment, toxicology and

potential side effects on the one side and optimal nanomaterial selection and positive effects on the other side is necessary (Linkov et al 2008). The toxicology of nanoparticles has already been confirmed by experiments on laboratory rodents. These experiments showed that high concentrations of nanoparticles can cause an asbestos-like reaction in the body of the rodent. Causing effects similar to that of chronic obstructive pulmonary disease (COPD) in the lung tissue (Oberdörster 2010). The risks of the usage of nanomedicine and nanoparticles when unchecked is, according to these experiments, pretty extreme.

These results should however be viewed with a certain amount of caution. Not only because these are results of test on lower life forms, which might react differently to the nanoparticles then humans, but also because most test are based on the administration of high dosage over a short period of time (Oberdörster 2010). The normal dosage of the nanoparticles is much smaller and is spread out over a larger period of time. The effects of prolonged exposure to nanoparticles are therefore still unknown and further research into the subject is advisable before a final verdict on nanomedicine is given. In order to gain a better insight and produce the most reliable results the research on nanomedicine and nanoparticles will have to be done differently. According to Linkov et al (2008) the correct way of researching the field of nanomedicine is through a multi-disciplinary approach (figure 4). This means a combination where toxicology, risk assessment modeling and multicriteria decision analysis (MCDA) tools are needed in order to take all aspects of the problem into account and give a better understanding of the basic interaction between nanoparticles and living cells and

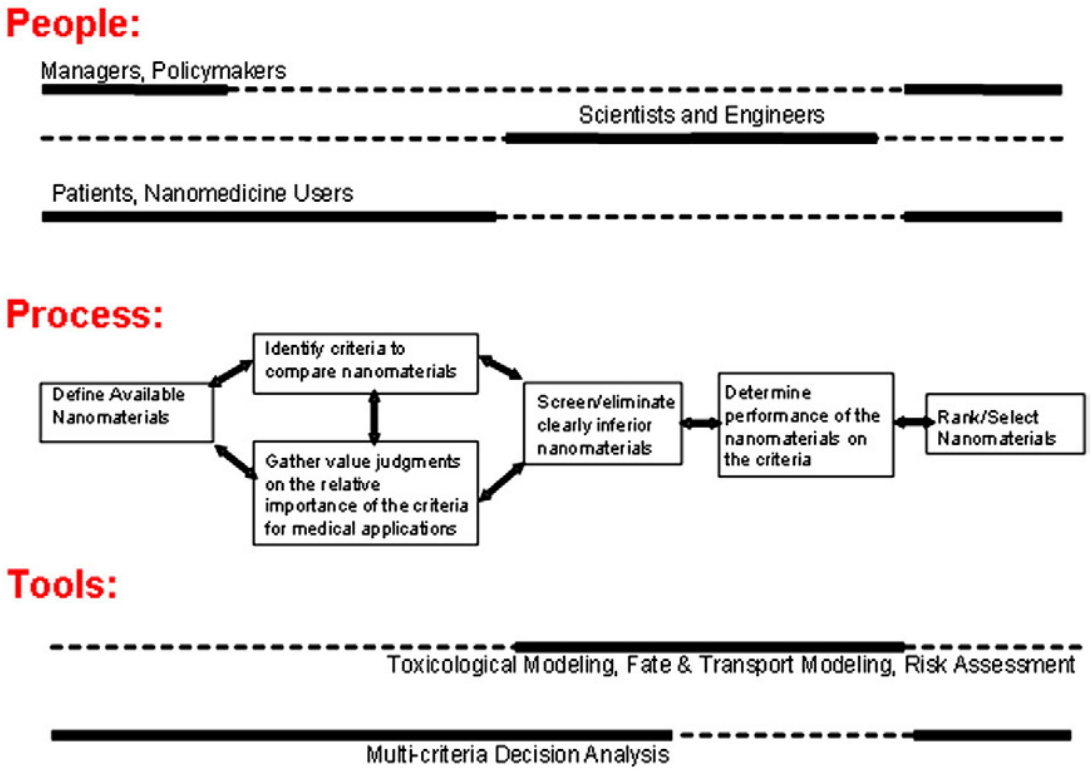


Figure 4 A representation of a decision process using the MCDA principle (Linkov et al 2008).

organisms (De Jong & Borm 2008). The use of MCDA tools will be necessary in order to combine the knowledge of experts from various fields and other sources of data and synthesize them into a framework that can be used to evaluate procedures and alternatives, as shown in figure 2 (Linkov et al 2008). This framework will not only take into account the effects of certain nanomaterials or particles, but will also look at risk assessments from different experts and even data on alternatives. The use of an MCDA-framework will help manage the existing risks that are associated with nanomedicine, but will also be able to handle future problems because of its ability to handle heterogeneous (different kinds of) information.

Which benefits can be derived from the use of Nanomedicine?

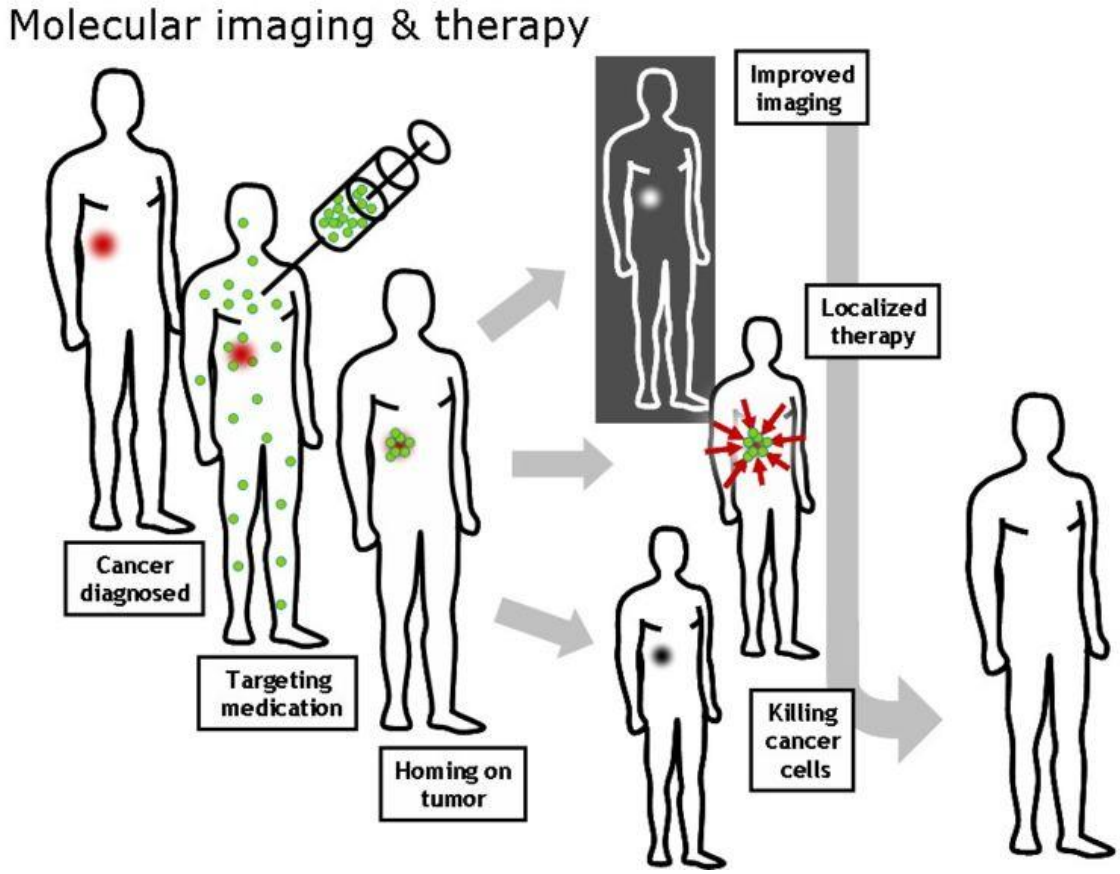
As seen in the previous chapter, the different ways in which nanomedicine can be used are quite versatile. This versatility and the many differences also create a certain amount of risk, not only directly to the patient, but also indirectly to say the environment (Faunce 2007). Be that as it may, the amount of risks and potential downsides is most likely only a fraction of the potential achievements and improvements that nanomedicine can cause for the field of medicine and even humankind as a species (Oberdörster 2010). But let us nog get ahead of ourselves, because the day when nanomedicine will be used to cure any illness or repair any biological of physical damage to the body is still a long way off. For now the benefits of nanomedicine are still somewhat smaller and most procedures are still in their experimental stages, which makes it unclear whether it will be solely positive results or not (Khushf & Siegel 2012). This chapter will therefore focus itself on the benefits that have been derived from research and practice, but a distinction will be made between direct (diagnostic and therapeutic) medical benefits and the indirect benefits.

Diagnostic and therapeutic benefits

The direct medical benefits are those concerning the wellbeing of patients and the improvements that can be expected in the medical field because of nanomedicine. These can range from diagnostic benefits to therapeutic benefits and every field in between (Morrow et al 2007). Using nanotechnology and nanoparticles is possible in almost every medical field, not only because of the great versatility of the particles, but also because of their microscopic size.

One of the main fields that benefits from nanomedicine will be diagnostics. At the moment the field of diagnostics is benefitting greatly from improvements in the field of Magnetic Resonating imaging (MRI) and Computed Tomography (CT). There is however only so much that an MRI or a CT can do, before it is troubled by things like background radiation. This is where nanomedicine can offer a solution, because it promises sensitive and extremely accurate ways for *in vitro* and *in vivo* (in vitro is the work inside glass, for example in test tubes and in vivo is inside the human body) diagnostics and imaging, far beyond the capabilities of today's state-of-the-art MRI or CT scans (Duncan & Gaspar 2011). The main goal for the field of diagnostics is that they can identify a disease as early as possible. The aim of nanotechnology and nanomedicine is to make diagnosis and treatment possible at the cellular and even the sub-cellular level. Using a technology called "quantum dots" it is possible to study cell processes at a molecular level, one molecule at a time. Using these dots it is possible to make an extremely detailed and visible image (figure 5) of for example

Figure 5 the way quantum dots can be used in cancer treatmet (Duncan & Gaspar 2012).



the location of a tumour. Therefore making it possible to treat the tumour, and only the tumour, in a much earlier stage (Hock et al 2011). Using nanoparticles for diagnostic procedures and imaging technologies can create a gigantic leaps forward in the way we view and research our bodies and other tissues. There is however a downside to the use of nanoparticles and the so called “quantum dots” and it is something we have seen in a previous chapter (Oberdörster 2010). These particles come with a certain toxicological hazard that can pose a great risks to the host body, because they need to be intravenously in order to work. For now this is one of the bigger downsides, but nanomedicine also has a possible way to deal with this itself and that is using other non-toxic particles to coat the “quantum dots” and eliminating their toxicity (Moghimi et al 2005). Needless to say that the possibility to accurately map the human physiology, inside a living body, is extremely valuable in the understanding and detecting of many kinds of diseases and ailments.

But using fluorescent nanoparticles is not the only way nanomedicine is benefiting the field of diagnostics. The development of biochips is one of the more promising fields of research in the field of medical diagnostics. A biochip is a microscopic piece of hardware that has numerous biologic sensors embedded into its structure (Morrow et al 2007). These sensors are able to detect anomalies and can later be read by the diagnostician. The further advancement of nanotechnology and the field of nanomedicine is being used to increase the

density of such sensors on the biochip and to create alternative detection mechanisms (Hock et al 2011). Making the effectiveness and possibilities of a single biochip much more versatile, which in turn lowers the amount of biochips needed inside the human body in order for the diagnostic procedure to work. Needless to say that the lower the amount of biochips needed to attain the desired result or data, the better it is for the patient and the less likely he or she is to react to the procedure in a negative way.

The therapeutic benefits of nanomedicine are also not to be underestimated. The advancements and research into new therapeutic procedures is one of the biggest and costly industries in the world (Morrow et al 2007). The development of nanomedical procedures will introduce a whole new range of therapeutic possibilities. The benefits of nanomedicine in therapeutics will be the most significant in the usage of drug delivery methods and regenerative medicines. Drug delivery methods imply that nanoparticles can be used to better target drugs at the source of the disease instead of the symptoms, which increases the efficiency and minimizes the side effects. Apart from that nanomedicine can also be used to achieve a controlled release of therapeutic substances (Duncan & Gaspar 2011). Regenerative medicines are nanoparticles that are used to manually activate and stimulate the body's innate repair mechanisms. A way to achieve this is by activating and controlling the adult stem cells, using an artificial agent (Duncan & Gaspar 2011). Of course there are many other advancements in therapeutics such as: using nanopeptides that support cell growth to repair spinal cord damage, special enzyme-sensitive nanocoatings that specifically target brain tumours and special nanoparticle probes that are capable of drug delivery on an intra-cellular level (Morrow et al 2007).

So let us first take a closer look at the methods of drug delivery that nanomedicine can offer us. The aim of this technology is to create a "vehicle" that can transport the necessary drug to a specific location. Not only because the drug has a better chance of achieving its desired effect, but also because it will be much more efficient, meaning the dosage can be cut back (Duncan & Gaspar 2011). Apart from that these nanoparticle vehicles (figure 6) can be used

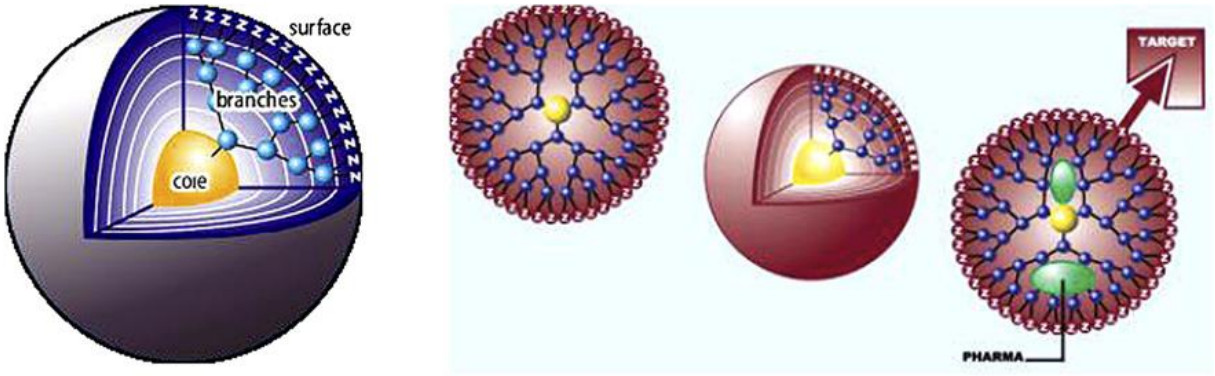


Figure 6 a visual representation of a nanoparticle drug delivery housing (Morrow et al 2007).

to not only house the drug, but also to release it at a specific moment or interval. This form of controlled drug delivery and release shows great potential, because it can be controlled using magnetically activated nanoparticles or sensory particles on a biochip (Chowdhury 2010). This in essence turns the nanoparticle, with the drug inside, into a miniature medicine supplier that not only monitors the dosage but also the concentration of the drug in the system and releases the drug only when necessary.

The benefits of regenerative medicine are substantial, because they combine our body's own ability to heal itself with the added power or effectiveness of a more specific cure. The idea behind regenerative medicine is that a nanoparticle transporting a certain genetic code or DNA-sequence is transported to a stem cell and then deposits its payload into this stem cell. Thus prompting the stem cell to take on specific properties or commence specific actions which will turn it into the cells that are needed to repair the physical damage (Zarbin et al 2012). This procedure can also be done on other types of cells or even glands so they release the correct amount of hormones or enzymes, therefore making it possible to treat all kinds of chronic and degenerative diseases. These diseases have a great impact on the quality of life of a person and also on the healthcare system as a whole, if these can be eradicated then this would benefit the medical field greatly. But it would also mean a massive boost in the overall quality of life in society (Zarbin et al 2012).

Indirect benefits

As far as medical benefits go the sky seems to be the limit, given an ample amount of time and research possibilities. There is however a second kind of benefit for us that can be derived from the development and use of nanomedicine. These indirect benefits are mostly in the form of economics and availability (Moghimi et al 2005). The pharmaceutical industry and the medical industry are both good for millions if not billions each year on costs. These costs are used not only to manufacture existing drugs and procedures, but also to research new and improved methods. The advancement and development of nanomedicine is among this research, but for the moment this is largely dependent on the amount of government funding that goes into research (Morrow et al 2007). Industry's and governments are beginning to see the potential that nanomedicine has and are actively encouraging the private sector to also get involved an to invest. When this finally takes hold, nanomedicine and nanotechnology will become a blossoming source for corporate investment and revenue (Morrow et al 2007).

Nanomedicine will be able to replace many of the current day medicines and procedures. Take for example the costly procedure known as chemotherapy. Creating the agents and fluids that are used in chemo is a very precise and expensive business. With the proper

application of nanoparticles and nanomedicine however, this type of therapy will become almost obsolete (Duncan & Gaspar 2011). The benefit that of nanomedicine will not only be medically in the form of a safer and more effective treatment, but will also be financially and ecologically beneficial. Using nanoparticles instead of chemo fluids will be more cost-efficient, because the amount of hospitalization time and chances of further illness are drastically reduced, which means that the amount of additional costs will be much lower. Apart from that the ecological/economical advantage of nanoparticles is abundant, because they can be retrieved and recycled. By retrieving and recycling them there production costs are relatively low and their ecological impact is virtually non-existent (Morrow et al 2007; HCN 2011). If this is done properly then the costs that will be saved are tremendous and may completely outweigh the costs associated with the research and development of nanomedicine.

How should nanomedicine be conceptualized in health law and ethics?

The benefits and risks that can be associated with nanomedicine are as diverse as the amount of applications and possibilities that the technology offers. Because of this diversity both in types of application and risks associated with these applications it is virtually impossible to determine one common pitfall that we should look out for when using nanomedicine. In reality the development and implementation of nanomedicine is more like a minefield, where some mines turn out to be duds, while others can turn into a gigantic catastrophe with far reaching consequences (McHale 2009). In order to better navigate through this minefield it is necessary to follow the laws and regulations that are already in place, but it may also be necessary to change them or create new ones in order to guarantee the safety and quality of the procedures. Laws are there to protect us (from ourselves), but are not always fool proof or just (Faunce 2009). That is because laws are not always in harmony with our morals or our values, which can lead to a so called ethical dilemma. The role of ethics is therefore equally important, especially with a subject such as nanomedicine. In the following chapter the subject of nanomedicine will be reviewed from both the field of health law as well as the field of ethics.

Nanomedicine in health law

The concept of nanomedicine is relatively new in the medical world. It was first introduced a few decades ago and was thought to have developed much more by now, to a stage were most risks and problems would have been overcome (Moghimi et al 2005). It came however with a certain amount of risk and uncertainty. This uncertainty is one of the main reasons why there are no specific rules and regulations for the fields of nanotechnology and nanomedicine. The legal field is largely dependent on legal certainty and this certainty about the rules and regulations is one of the building blocks of the European medical regulation policy. Without this certainty, or evidence, the laws are not made, because without a firm and certain basis a law has no principle to uphold (Toma-Bianov 2012).

The uncertainties that have to be addressed are made up of four different problem areas: the ambiguity over classification, the manufacturing method, the development procedure and the safety issues (Kelly 2010). The first problem area, ambiguity over classification, is one that effects the entire research field and makes it virtually impossible to give a general definition of the term nanomedicine. Seeing as there is no general definition for the term nanomedicine. First of it is unclear whether nanomedicine should be classified as a medicine or a medical device. The problem here is that the primary goal of a product also dictates which regime or laws it falls under. If nanomedicine was defined as a medical device than that means that its function is fulfilled by physical means or chemical actions, meaning a

direct result of an action. The definition of a medicinal product states that is primary goals is achieved by pharmacological, immunological or metabolic means, meaning the body reacts to the drug and creates or delivers the medication (Kelly 2010). The problem of this modus operandi is that both the definition of a medical device and the definition of a medicine are applicable to certain types of nanomedicine. Therefore it is unclear which rules and regulations are relevant for nanomedicine, half, both or none. According to Duncan & Gaspar (2012) the key is to be flexible in the way that the legal criteria are met, but they are actually not meant for a field such as nanomedicine. As if this difference in application definition wasn't enough, there isn't even a general consensus concerning the international definition of nanotechnology and nanomaterials (Kelly 2010). Because of this it is unclear what can be classified as "nano" and what not.
So if there is no standard for both its classification (the what) and its function (the who) then it is not possible to apply the current laws and legislations, expect for the most arbitrary and common ones. Such as the EU directive on human medicines (2001/83/EC), the Medical Devices Directive (93/42/EEC, as amended) and the European Commission (EC) regulation on Advanced-therapy medicinal products (ATMPs) (1394/2007). These three regulations are however only applicable to a basic extent and can therefore not solve all the legal issues, without a certain amount of adaptation or even the creating of new addendums.

The second problem area is the manufacturing method. Most of the manufacturing methods and challenges are based on the production of conventional medicines (stability, limits to process impurity and an optimised manufacturing process to achieve the desired drug particle distribution within the product) and also apply to nanomedicine (Trisolino 2010). In order for regulatory committees to give out a license for manufacturing, the medicine always has to be characterised first. There is however still no "golden standard" for the characterisation of nanoparticles which makes most regulatory agencies reluctant to give out manufacturing licenses (Kelly 2010). And without a mandatory license for manufacturing it is forbidden to create the medicine, so you can imagine that this creates certain problems for developers and researchers.

The third problem area is the developmental procedures. The development of nanomedicines is still a very new area of research. And there are a still a few issues that need to be addressed in order to create a one-size-fits-all approach to for example effects on the immune system, the genotoxicity and the physic-chemical characteristics and stability (Mchale 2009). For the moment there are only general risk assessment guidelines that are applicable to conventional medicine. The undefined nature of nanomedicine, as discussed in the previous chapters, makes it difficult to evaluate the effect of the medicine on any other than a case-by-case evaluation. In order to make any real progress it is proposed to create a

nanomedicine specific guideline, in which all of the nanomedicine specific effects and difficulties handled (Kelly 2010). The most easy way to do this is to adapt the existing regulations to also encompass the nanomedicine specific issues, instead of creating new guidelines. Creating new guidelines is much more time costly than adapting existing ones, but may prove to be the only possibility in the future (Toma-Bianov 2012).

The fourth and perhaps most important problem area is that of the safety issues. Despite recent advancements and the billions that are being pumped into research, many information regarding the interaction between nanoparticles and biological systems and the effects at a subcellular level are still largely unknown (Kelly 2010). What is known is that there is a big difference between the different nanoparticles and the way they react to living cells or the effects they have in comparison to the chemical they are made of. This difference can be the difference between an easily soluble nanoparticles which is broken down in the bloodstream and one that doesn't break down and builds up in the system, causing a disease or an infection (Trisolino 2010). The characterisation of the different nanoparticles and materials is therefore necessary in order to better understand the effects and reactions they can have. This is mandatory to be able to incorporate the nanomaterials into a risk management plan. A complete risk management plan of the nanomaterials is needed to gain approval for development. The relevant legislation that determines approval is the EC directive relating to medicinal products for human use (Article 8(3) (ia) of directive 2001/83/EC, as amended). In order for this risk management framework to be applicable for nanomedicine the framework has to be adapted to include other types of toxicities, such as the nanotoxicology. These are specific risks that do not fit within the current regulatory frameworks (Kelly 2010).

Because of these four problem areas the future of nanomedicines and the laws and regulations concerning them will have to adapted and specified in order to cover all aspects. This challenge will not only have to be addressed on an international level, but also on a national level (Mchale 2009). The laws and regulation have to be made in such a way that specific risk evaluation is taken into account, that this evaluation is undertaken in a scientifically sound and transparent manner, that the rules and regulations are made clear in certain areas where the regulations overlap and that the ethical dimensions and the fundamental human rights also need to be taken into account because they above all need to be safeguarded (Mchale 2009; Toma-Bianov 2012). Adapting the Dutch laws and legislations in order to cooperate the different aspects of nanomedicine is not enough to create a safe future development for this field of research. Because of the nature of nanomedicine it is becoming ever more important to form an international legal background in order to rise to the challenges of a technology that is being researched on a global scale

(Trisolino 2010). Nanomedicine will therefore have to be incorporated on an international scale that takes all legal possibilities, assessments and safety restrictions into account. Thus assuring a legislation and legal security and certainty that will help canalize the field of nanomedicine in the correct ways (Faunce 2009). This will make it possible to create a set of rules and laws that will create certainty for the nanomedical research field and will help the field of nanomedicine to more easily be implemented into the field of conventional medicine.

Nanomedicine and the ethics involved

Apart from the legal standpoints and the potential problem of safety issues that have to be incorporated into existing or newly created rules and legislations, the issue of society's ethical use of nanomedicine and nanotechnology is a different but nonetheless important subject. Ethics is therefore something that is intertwined with everything we do, it is a set of concepts and principles that guide us in determining what behaviour helps or harms sentient creatures (Paul & Elder 2006). The ethical issues that concern nanomedicine are similar in nature, but concern not only the thought if something helps or harms a sentient creature, but also whether the action is desirable even if it helps or cures. There are in general four ethical dilemmas concerning nanomedicine that have been put forward: (Lenk & Biller-Adorno 2007)

1. Risk assessment in medical research, diagnosis and therapy.
2. How to meet the criteria of informed consent
3. Questions of personal and human identity
4. The distribution of risks and potential benefits.

These four main ethical concepts are not completely specific to the field of nanomedicine. They have all been put forward before in the context of other technologies and procedures who have had to navigate through the ethical field (Bawa & Johnson 2007). It is however not wise to say that the ethical conflicts have all been resolved before or that nanomedicine is no different than other experimental medical technologies. The four main ethical issues are there because nanomedicine has similarities with other medical fields, but is also different in a fundamental way and that is that is has a connection or overlap to almost every other field of medicine in one way or another. The four main points will be discussed in some detail in order to explain this.

Risk assessment in medical research, diagnosis and therapy is something that is necessary in order to determine the impact a new technology can have and whether the amount of benefit it poses is greater than the perceived risk (Bennet & Naranja 2013). In theory a risk assessment is quite simple, the only things that are needed are the possibility of a certain event and the extent of damage that this event can have, meaning the chance and the outcome. In reality however there is a difference between a simple understanding of risks

and a more extended one. A more complete understanding of risk will also include things such the subjectively or objectively perceived effect on some ones quality of life, changes in social interaction or the unequal distribution of risks/benefits (Lenk & Biller-Adorno 2007). And depending on your point of view one will for example choose a higher amount of risk that is more evenly distributed among the populous, above a relatively lower risk which will only affect a small group of people. This more extended view of risk assessment is quite more difficult and will almost never have one unanimous result including all opinions. This extended form is however the most adopted among the medical field, because it also takes into account a more patient-centred approach of the ethics debate. (Lenk & Biller-Adorno 2007). This is very understandable, because for patient who are subjugated to a procedure or technology, the possible side effects of the effect the procedure can have on their quality of life are also important (Bawa & Johnson 2007) and not just the objective chance they have for risk and the extent of damage. Inside this medical ethical field there is a difference between two types of risk, the so called 'minimal risk' (a minor profit with a minor risk) and the so called 'greater than minimal risk' (a potential for great profit, but with greater risk). From a patients perspective these types of risk are usually favoured in a certain type of procedure. In therapeutic procedures people will usually take greater risks, because they can get better faster or can improve their health more substantially. In the non-therapeutic procedures, such as research, the preferred choice for a patient is mostly that of the minimal risk, because it might offer a slight profit or it might diminish the quality of life in a small way (Lenk & Biller-Adorno 2007). This difference is based on a rational choice from the patient and is based on that patient's morals, beliefs and ethics.
This difference between the therapeutic and non-therapeutic risks people are willing to take is one that is different for the field of nanomedicine, because nanomedicine, in most forms, is most of the time both at once. This combination of risks is something that may lead to unknown factors and unknown amounts of risks, were the effects can be predicted pretty accurately (Resnik & Tinkle 2009). The dilemma here is whether it is ethical to let someone make a choice solely on the possible effects or profits, without knowing the potential risks.

How to meet the criteria of informed consent is something that will also be difficult to accomplish. According to the Dutch medical treatment act, the WGBO, it is mandatory that a patient receives all the necessary information about a procedure or medicine before performed or given to the patient (Art. 7:450, BW). This criteria of informed consent is mandatory, except in a life threatening situation. With a procedure such as nanomedicine this may be even more important, because of the potential of unforeseen effects and the uncompleted overview of the risks (Resnik & Tinkle 2009). This is also one of the ethical dilemmas, because it is not only legally forbidden to perform a procedure without first

notifying the patient of all the possibilities, but is also against most morals and ethics. The problem with nanomedicine is that the information for the patient is very incomplete and has many unknown variables. This makes it very unclear if the obligation of informed consent can be fulfilled at all. Therefore is it possible to say that it is ethical to treat people with procedures and medicines that have been tested, but we still do not know of the full extent of effects and possible risks. In order to tackle this ethical debate a more prudent research and investigation into the possible risks and effects of the procedures has to be undertaken, but this could also prove that the extra risks are neglectable and the procedures could have been used to safe lives in the meantime. The question that comes to mind here is: Is it ethical to use a procedure without having complete knowledge of it?

Questions of personal and human identity are something that the upcoming of nanomedicine has put into a new perspective. Because the aim of nanomedicine is to cure or even improve the human body, sometimes strengthening its own functions or activating them, the question arises what really are the "human" functions and abilities. *"How can the body be distinguished from a technique which obtains its potential effectiveness exactly from the ability to imitate natural mechanisms and natural functions?"* (Lenk & Biller-Adorno 2007). With the line between "human" functions and that a machine or procedure can do becoming more and more blurred it will be increasingly difficult to say what is part of the human identity and what is not. Things like a pacemaker or an insulin pump were obviously not a part of the body, they were separate, and took over only a certain function, but when the same effects can be achieved by implanting a few nanoparticles that tell your molecules to regulate things more efficiently or take over the job of other cells it becomes a part of the body in a most drastic way. This can lead to a rapid change in what we see as our personal or "human" identity (Bawa & Johnson 2007). The innovations that nanomedicine can offer us, can change the way we view our live and that of the human species, without for example talking about the more futuristic "super human enhancements". A normal therapeutic method that would be capable of clearing our corroded arteries and such will eliminate one of the most common causes of death in our societies, thus having massive consequences for our population's age structure and what we consider to be a normal old age (Lenk & Biller-Adorno 2007). The effect that nanomedicine can have on what we perceive to be normal or part of the human identity can be monumental, nanomedicine is capable of changing what it means to be human. This change is view or change in meaning is something that will create an ethical dilemma in the form of a question: what does it mean to be human?

The distribution of risks and potential benefits is something that can prove to be difficult when trying to achieve a just distribution. The aim is that both the benefits and risks will be distributed evenly, so that everybody can have the same effects from an emergent

biomedical technology. The case however is that with most newly emerging technologies the distribution of these two is not usually very just (Resnik & Tinkle 2009). In the early stages most of the risks will be carried by a group of test subjects that has voluntarily agreed to participate in trials. This group of test subjects almost has to meet a certain set of criteria I order to be accepted, usually suffering from a specific sort of disease. From an ethic point of view it would therefore also be just if this group were the ones that got the most benefits out of it, seeing as they are running the highest risks. In reality however the first group of participants has a significantly higher risk than for example the second group of participants, while the potential benefits are still equal or even higher for the second group (Lenk & Biller-Adorno 2007). Because of this the goal must be to minimize the risks as much as possible and to create an as fair as possible distribution of the risks and benefits between the different groups. This is still very difficult because it usually takes up a lot of time to develop a new procedure or new formula for medication, participants of research who are suffering from degenerative diseases will most of the time not be able to enjoy the benefits of these new and improved procedures. This is what makes human testing and clinical testing an unethical way of practice, though it may be necessary, it actually isn't right.

"Right is right, even if no one does it; and wrong is wrong, even if everyone is doing it"
-William Penn-

A final problem is the entanglement of private enterprises in the field of nanomedicine. The outcomes and results of publically financed research are always published for everyone, even if it is against a nominal fee, but the results of privately funded research are not always available, because it is more interesting for an enterprise or company to keep the results for themselves. This is in fact a general problem in medical research today, but it is an even bigger problem for nanomedicine (Lenk & Biller-Adorno 2007). It should therefore be made mandatory that a regulatory framework is setup to safeguard the publics and especially patient's interest so that they may have an equal opportunity to benefit from the research.

What are the opinions expressed by expert stakeholders concerning the ethics debate of nanomedicine?

In the field of nanomedicine there are a lot of stakeholders that share an interest in the subject. From the physicians and practitioners to the private enterprises and the pharmaceutical industry, everybody wants to get a piece of the action and has an opinion on the subject (Lenk & Biller-Andorno 2007). The field of nanomedicine is an international field of research where joint efforts are taking place to let the technology progress and evolve in the best possible way. Trying to take into account all possibilities, concerns and safety issues is too much for one enterprise or organisation to handle. This is why around the globe multiple organisations and advice boards have been founded, containing the best and brightest minds in the field to further the cause of nanomedicine. One such board is the European group on ethics in science and new technologies (EGE) (2007). In this chapter a review will be made of the opinions that are most common around the world and that are being supported by the various support groups. This will be done from two different viewpoints, the bioethical and the social ethical.

The bioethical standpoints

Every area of science and/or new technology that is being developed within the European Union has to be consistent with the ethical principles that are stated in the European Charter of Fundamental Rights (EGE 2007). This charter is meant to protect the human dignity of every citizen both in positive means (raising the standard of living and upholding the rights) and in negative means (the right to be protected against unjustified risks or maltreatment of any form caused by the actions of others). In order to make sure that a new technology such as nanomedicine also lives up to these criteria an assessment has to be made regarding the safety, ethics (both individual and social), the economic and public principles and the socio-cultural anthropology (study of human past and present) (EGE 2007). This distinction however can raise some additional problems, therefore it is important to take into account that nanomedicine may have an effect on citizens indirectly (exposure to free nanoparticles) and directly in the form of trials and testing. This is the agreement of both the EGE (2007) and the American society for nanomedicine (ASNM) (Shils et al 2013).

The bioethical aspect of the ethics debate concerning the protection of individuals is focussed on the necessary regulations apart from those already incorporated into the international declarations and guidelines that apply to both healthcare and medical research. These include the obligation for free and informed consent from patients or trial participants and the possibilities and measures that have to be taken when someone is not mentally competent to freely give consent (EGE 2007). The declarations and guidelines as stated above also say that the individual has to be protected from any and all unpredictable risks.

Apart from the protection of the individual it has also been determined that the benefits and potential positive effects of nanomedical research have to be accessible to all and should be divided in the most equal fashion that is possible.

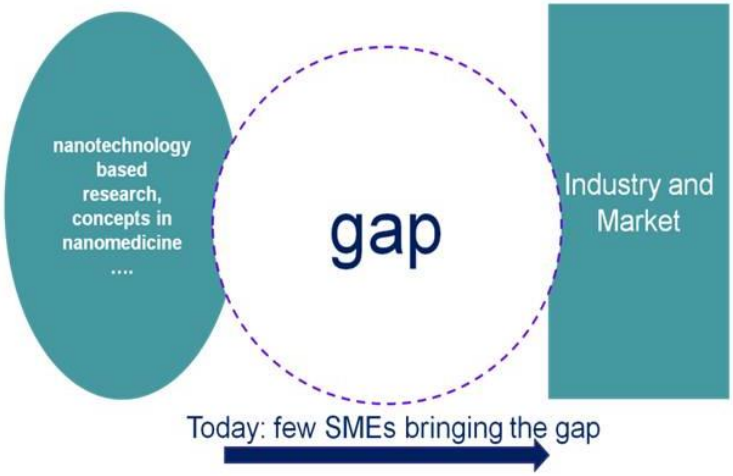


Figure 7 the information gap that exists between the research into nanomedicine and the actual markets (Costa et al 2011).

The difference between nanomedicine and other technologies is that with nanomedicine there are much larger gaps (figure 7) in the information and there are much more uncertainties at the moment than with other medical technologies. The primary aim should therefore be to overcome these gaps and gain as much information and knowledge about the subject, so that the protection of individual can be safeguarded (Costa et al 2011; Shil et al 2013).

In the case of nanomedicine informed consent may therefore be very difficult to obtain, because how is it possible to give understandable information when there are still as many unknowns and complexities that are not known. The providing of adequate information about a diagnosis, prevention or therapy needed, is at the moment still impossible for most nanomedical procedures, because there is simply not enough known about them (EGE 2007). It is therefore very important that a distinct difference is made between invasive and non-invasive procedures, because their respective risks are completely different to start with. Apart from this nanomedicine does offer new possibilities and potential for the field of diagnostics. The results of these new and improved diagnostics may however be difficult to interpret and the speed with which people will have to interpret and understand the results will be much faster. The methods and regulations needed to handle this greater personal responsibility have however already been discussed extensively in the context of genetic testing (EGE 2007). The improved precision and speed that nanomedicine can offer in this field will enhance the amount of personal freedom and possibilities that a patient will have, in theory. In reality however it can also create greater feeling of responsibility with the patients

which in turn leads to a shift of responsibility for the patient's health from the doctor to the patient himself (Costa et al 2011). Tis increase in personal responsibility can lead to anxiety and problems for some patients and must therefore be meticulously controlled and monitored.

The more refined and detailed information about a patient that can be gathered using nanomedical technology is also something that can be used by third parties, such as employers or pharmaceutical enterprises. This information can be used for two purposes, both to construct better tailored plans for patients, so that there care will improve (EGE 2007). It can however also be used to take advantage of certain patients or be used to select which patients should be treated of insured and which shouldn't, with regard to expected costs. It is therefore mandatory that the information collected from nanomedical procedures is restricted to those who work with it, but can adapted before it is released for public access in order to further the scientific community (Shil et al 2013). The other potentially ethical problem that can arise is that there is an extremely fine line between medical and non-medical potential. The non-medical application of nanomedicine is for not medically necessary purposes and may include enhancements of the body. These non-medical enhancements are however capable of producing and relaying information about the human physiology that can be used for medical purposes (EGE 2007). The problem this poses is that with the evolvement of the nanomedical field the plurality of lifestyles for the individual as well as the states can disappear and we can come to a stage were the medical system will transform into more of a service system, were individuals can not only go to satisfy medical desires, but also many non-medical things like human enhancement and other improvements that will greatly diminish the human diversity.

From a bioethical standpoint the possibility for access to health-care and new medical technologies is already one of the greater challenges. Individual may go to great lengths, financially, to gain access to nanomedical procedures and innovations. If an individual is not able to afford the access to nanomedical procedures, than that individual can feel left behind or even a second-class citizen (EGE 2007). This can also be seen as a form of discrimination or injustice, when there is a difference between the availability and the possibility to use the technology in concrete life. This ethical issue of inequality has to be taken into account before a society can develop were only a portion of the people can benefit from the advances of nanomedicine (Costa et al 2011).

Social ethical viewpoint

The opinions on social ethics are divided between economic, socials and public concerns and issues concerning governance and institutions. The opinion that has been put forward

by the EGE (2007) is that research into new technologies should be incorporated into the strategies for economic growth and development not only for the separate countries, but also for the governing bodies, such as the EU. When the possibility for research and development is stimulated in this way that it will gain a boost and will also be of profit to the governments. The expectation is that by 2015 the amount of money the nanotechnology market will be worth will exceed one trillion, on an annual basis. And the market for nanomedicine is already estimated to be worth about 260 billion, worldwide. Investing in research and implementing the development into the strategies will be necessary in order to keep nanomedicine, at least partly, in public hands. Thus safeguarding the public access.

The social and public concerns that should addressed are numerous, but are not unable to overcome. Pluralism is one of the foundations of our society, not only on a national level, but also on an international level. Respect for this form of pluralism is and respect for multiculturalism is one of the foundations of the EU. The EU has even already taken steps to develop ethical standards that guide decisions in the medical field within the moral constraints that are fundamental for western society: the principle of respect for the individual and its rights, respect for multiculturalism, dialogue and tolerance (EGE 2007). These already present standards actually stimulate the evaluation of new technologies and procedures and provide additional criteria to further test the new medical technologies. Because of this plural society it is also a vital concern that the public is involved in the decisions that are made about the ethical concepts that are associated with nanomedicine. Public participation and discourse is important to implement (figure 8) new and emerging technologies (EGE 2007). In order to create the interaction between the public and the scientific and decision-making community, it is possible to host things such as open conferences, communication tools for the public and surveys. Participation of the public is necessary not only for the reaching of a general consensus, but also to create strategy where public concerns are discussed from the beginning, so that this innovative research can be better developed and implemented.

Figure 8 a cartoon depicting the difficulty of implementing new guidelines

The opinions regarding the approach to nanomedicine that institutions and governments should have is that of an instigator. Governments and institutions should strive to improve the relationships between society and the economy and research institutions (Shil et al 2013). Each state on its own must first of all safeguard the basic rights of individuals such as human dignity, protection of privacy and confidentially of personal information, personal autonomy and integrity. These basic rights need to be safeguarded at all cost, but with the coming of nanomedicine the line between the information gathered from procedures and that of a more personal nature is getting thinner and thinner (EGE 2007). So where do you draw the line and how do you implement strategies to protect an individual's privacy and dignity, without hindering the process of new medical technologies? This is an ethical subject that has to be reviewed more thoroughly, because there is no strategy as of yet that can take everything into account. There are however already certain rules and regulations in place that are meant to manage the use of new technologies in the medical field and general applications of new forms of technology. Individual states and international organisations will also have to find a way to follow the rules that are already in place, but also find a way to incorporate a more advanced and extraordinary technology such as nanomedicine (EGE 2007; Shil et al 2013). Nanotechnologies and nanomedicine also have major application in the fields outside of individual and public health. The regulatory issues that this implies can arise at different levels, such as the research and testing of new drugs, but also with the development of other new technologies (EGE 2007). The relationship between the freedom and integrity of every individual citizen on the one hand and the development and use of commercial technologies on the other raises issues that have to be settled politically and have to be taken into account when creating new regulations that affect the field of nanomedicine.

In order for nanotechnology and nanomedicine to be implemented properly the guidelines for clinical research will have to be adapted. This is because the usual guidelines for clinical trials and research ethics (CIOMS 2002) is only meant for the current clinical techniques. For the field of nanomedicine it may prove rather difficult to meet some of the requirements set by the current guidelines. Especially the guidelines concerning patient data and general data protection, because in comparison to other fields of research, in the field of nanomedicine the information about patients and the information received from clinical testing is available to a large group of specialists (EGE 2007). This is because nanomedicine is a research area that has a large overlap with other fields of research.

As you can see the opinions on the field of nanomedicine and the way that it should be regulated are actually all aimed at the same goal. The goal is to create an ethically responsible regulatory framework that will be able to encompass all ethical issues. From the

safeguarding of human rights and the ways to respectfully implement the technology into society, to ways of guaranteeing the general safety of all, minimizing the risks and creating a platform so that future technologies can be more easily developed and implemented into the field of conventional medicine. The world best and brightest in the field of nanotechnology and nanomedicine agree that it is a technology that can have unlimited potential, but it has to be regulated in such a way that the risks will be regulated and minimized, the benefits will be equally distributed, the advancements and scientific progress should be available for the public domain and above all the rights of all humans must be guaranteed and kept safe.

In what way are there discrepancies between health law and ethics, concerning the field of nanomedicine?

As you have seen in the previous chapters, nanomedicine and the nanotechnological field are of a very different nature than other fields of technology or medical applications. Because of this different nature and the only short period of existence that this field of research has, there are still no actual regulatory frameworks designed specifically for nanomedicine. There is however an abundance of ethical issues that are concerned with nanomedicine. Some of these are similar in nature to those of other technologies, such as gene therapy, but the most prominent ethical dilemmas are something that are specific to nanomedicine. The combination of an absence of specific rules and regulations and the abundance of ethical concerns is something that should be handled with care. The aim should be not just to go for the most expedient way, but also the right way. Doing the right things, to the best of your abilities, is something that the field of health law is based upon. That is why this chapter will be divided into different sections that will evaluate the Dutch health laws in comparison to the current ethical concerns of nanomedicine. A distinction shall be made between the Dutch Medicines- and Health-act and the Dutch medical treatment act.

The Medicines- and Health-act and the ethical discrepancies

In the Dutch law system there are several specific boards and groups that are meant to govern, control and evaluate the Dutch and international healthcare. Two of these are the college for the evaluation of medicines (CEM) (Art. 2 Dutch medicines act) and the Dutch health board (Art. 21 Dutch healthcare act). The function of the CEM is to evaluate whether a new medicine may be eligible for a trading permit and distribution, the execution of European decisions regarding medicines and to provide scientific advice and information regarding the clinical trials, safety, quality and usefulness (Art. 9 Dutch medicines act). This in comparison to the function of the Dutch health board, which is to inform our government about the current standard of science concerning the fields of public health and healthcare by means of research reports (Art. 22 Dutch healthcare act). Although these two both have a different task, they can both have a quite substantial effect on the way that nanomedicine can or will be incorporated in the future.

In accordance with the Dutch medicines act any form of medication first must have a permit to be produced or shipped into the Netherlands (Art. 18, paragraph 1; Art. 40, paragraph 1 Dutch medicines act). The decision whether or not any form of medication gets a permit is up to the CEM and the minister of health, welfare and sport (HWS). In order for them to make these decisions they are dependent upon the information and knowledge that they gain from the fields of research into the subject. This is precisely where the first problem

might arise between the ethical concerns and the legal aspects. It is ethically responsible to only take a decision such as that of the CEM or the minister of HWS when all the information concerning risks and potential side effects of a medicine is available, so that the decision made is not only thought trough but also justifiable (Glenn & Boyce 2012). The current level of knowledge and the amount of information about these facets of nanomedicine is currently not extensive enough to say that a decision such as this will be absolutely rational. Because not only are there many undocumented risks, there is also a chance of unexpected and unforeseen risks caused by the interaction of the nanoparticles with other biological substances, that is still quite substantial. Not to mention the potential chance of long term risks or side effects that might occur (Trisolino 2010). Despite the fact that most knowledge about nanomedicine and its potentials risks is still uncertain, a few forms of nanomedicine are already being used and have been approved (Trisolino 2010). Therefore it is safe to say that this raises an ethical dilemma, because how can the production and distribution of something already be approved, without there being full knowledge of the possible consequences or long term side-effects? Legally speaking the use of these types of nanomedicine is already allowed by a board such as the CEM or our minister of HWS, but ethically speaking it is quite difficult to say that this is the “right” course of action.

Aside from this it is the responsibility of any manufacturer or producer to create the medicines or medicinal products they have in accordance with the requirements of good practice that have been put forward by the ministry of HWS and the CEM (Art. 27, paragraph 1 Dutch medicines act). This set of requirements is based on the knowledge of what is and what isn’t considered as good practice in the manufacturing of a certain form of medicine. In the case of nanomedicine there is however still no so called “golden standard” to the way that nanomedicines or even nanoparticles should be produced (Kelly 2010). There are however already a certain amount of ways that can be used to produce specific nanomedicines, but most somewhat differ, though the end result is the same in essence (Mchale 2009). The problem in this case is that according to the law, the manufacturing of a medicine or medicinal product has to be in accordance with the requirements regarding good practice, put forward by the ministry. At the moment however it is still not possible to say which procedure is actually the best. So it is almost impossible to create a set of requirements that dictates which manufacturing method is good and which is not. As mentioned before, some forms of nanomedicine have already been approved for production (Trisolino 2010), but this approval has been made without there actually being a form of production that can be dubbed as the best form of practice. Therefore the nanomedicinal usages that have already been approved present an ethical dilemma of sorts. The fact that they are produced in different ways makes it difficult to predict what the effects of this might

be in the future. The ethically correct thing to do is make sure that only the best form of practice is used so that the risks for our society are minimised and the potential benefits are the same for everyone that uses said medicines. The rules about the requirements of good practice as described in Art. 27, paragraph 1 (Dutch medicines act) are therefore not being lived up to in the case of these already approved medicines, but some are nonetheless being manufactured and used.

The Dutch health board is one of the administrations that concerns itself with healthcare research and is, as mentioned before, tasked with researching and establishing the current scientific standard of medicine. This is where the field of nanomedicine poses a difficulty as it is still impossible to incorporate its effects into a medical standard. This mainly due to the fact that there is still not enough information regarding the risks and possible (side-)effects, but also because there is still no official guideline for the field of nanomedicine (Glenn & Boyce 2012). In order for this guideline to be produced, in accordance with the CIOMS (2002), the Dutch health board will first have to research this and put forward an advice regarding nanomedicine. The amount of time that goes into creating a specific guideline such as this can be quite substantial, the development and research in the field however does not stop during this time. In the case of nanomedical research this is even more painstakingly obvious, in a period of only a few years the scientific community has made massive leaps forward (Glenn & Boyce 2012) and not a week goes by without some form of nanomedical research reaching the papers. Although this amount of progress is great news for the scientific community, it creates a great problem for an administration such as the Dutch health board. Because in the time it takes them to produce an advisory report, or a specific guideline to be formed, the field of nanomedicine may already be more advanced than specified in the advice or guidelines. The effect of this can be that the advice put forward by the Dutch health board or the guideline that is made, is no longer in accordance with the current scientific standard of that specific field. So the question that this poses is whether it is safe to create a standard or guideline which will ultimately always be one step behind the current events? From a legal standpoint this is not a great problem, because if the guideline or standard has been approved and validated than it is valid and the same goes for scientific protocols (Art. 2, paragraph 1 medical research involving human subjects act). As of yet there is however no guideline or standard regarding nanomedicine (Glenn & Boyce 2012; Bennet & Naranja 2013; McHale 2009) and even by creating a guideline or incorporating the field of nanomedicine into the current standard of medicine there will still be an issue that is specific to the field of nanomedicine. The progress rate of this field of research is so immense that any sanctioned or official guideline will always be one step behind the facts, causing a difference between what is allowed and what is possible. The

ethical dilemma here is that with a new procedure, that has been proven to work but has not been incorporated or allowed yet, the possibility of someone dying because of a technicality becomes possible (Hock et al 2011). This is something that has to be taken into account when the medical standard is reviewed or a new guideline is put forward, apart from every other legal aspect.

The medical treatment act and the ethical discrepancies

In the Dutch medical treatment act the rights and obligations of a patient are recorded. Apart from that also some of the rights and obligations of the medical practitioner are recorded in here. Think of rights such as that of doctor-patient confidentiality (Art. 7:547 civil code), a responsibility clause (Art. 7:462 and 463 civil code) and the necessity of informed consent (Art. 7:448 civil code). The latter is also one of the bigger problems between the field of health law and that of nanomedicine. With a procedure that involves nanomedicine or nanotechnology it will be difficult to meet all the criteria necessary to ascertain a legal form of informed consent from a patient. Two difficulties can arise when dealing with the necessity of informed consent and the relatively new field of nanomedicine and these are: how can a doctor or practitioner make everything clear to a patient and what the possible effects and risks are in regard to the patient (Art. 7:448, paragraph 1 and paragraph 2, sub b civil code). The difficulty of making it clear to a patient what exactly a procedure is or exactly what is does is something that can always lead to difficulties with the more complex procedures. This is because there exist a large gap, called information asymmetry, between the patient and the physician (Bloom et al 2008). Because of this information asymmetry a procedure can be quite difficult to comprehend for the average patient. Getting a patient to understand the procedure to a satisfactory extent can be very difficult to achieve (Bloom et al 2008), but in the case of a nanomedical procedure this difficulty is increased greatly. The problem of nanomedicine is that in order to understand it completely one has to have a very extensive knowledge of several research disciplines and the way these interact. For the average physician this will be quite a challenge all on its own, but for a patient to comprehend how a nanoparticle can transport a drug particle past his blood-brain barrier and the resulting effect this has on his or her body is just too much (Trisolino 2010). Therefore it is very important that the basic information and the vision associated with the nanomedical field are communicated and shared with the general public. This in order to raise awareness for the potential of nanomedicine, but also to involve society with this field of research (McHale 2009). Informing a patient about a procedure or type of medicine that has already been seen on the news or that someone has already heard of, will be much easier to do than trying to explain something that is completely unknown. Getting the public involved or making the information about nanomedicine more freely available will also help to reduce the amount of

information asymmetry there is (Bloom et al 2008). Thus ensuring that the cooperation of a patient will be more freely given and the patient will also have a better knowledge of what a procedure entails. Making a procedure clear for a patient is something that is ethically correct, because people have the right to know what will happen to them. In order to make sure that this is done not only because it is legally necessary, but also because it is correct, the public should be more involved in this innovating research field and the practitioners and physicians should be instructed about the potentials benefits and usages that nanomedicine can bring (EGE 2007). This way both parties can work towards each other, thus facilitating the way that informed consent is given and/or achieved.

A big part of the informed consent is the explanation about the possible risks and effects that a procedure can have on the patients' body (Art. 7:448, paragraph 2, sub b civil code). As has been mentioned before, the amount of information available on nanomedicine and the potential risks and side-effects that are associated with it are still largely unknown (Glenn & Boyce 2012). Achieving informed consent, without coercing the patient or the necessity of a certain procedure, is therefore impossible at the moment. The amount on unknowns and potential future risks is simply too great to give the patient a complete overview that is needed to give a fully informed form of consent. In order to satisfy the legal obligation, but also to do the correct thing ethically, it will therefore be necessary that all risks and benefits associated with a procedure are first known before the procedure is presented as a possible option for a patient (McHale 2009; Glenn & Boyce 2012). There is however an exception when the patient chooses to give consent, despite of the absence of the information about further risks or when the immediate benefits outweigh the possible risks in the future. For example when a nanomedical procedure will be the only possibility to save someone's life, but the potential risks this may pose in the future are unknown.

Apart from the informed consent there is also the matter of doctor-patient confidentiality that might become endangered because of a technology such as nanomedicine. According to Art. 7:457, paragraph 1 (Dutch medical treatment act) a physician or treatment officer is not allowed to give out any form of personal or medical about the patients in his care, except without express permission from the patients itself. An exception to this is made for concerns of public health and research or for any other medical practitioner that is involved in the treatment of the patient (Art. 7:457, paragraphs 2 and 3 and Art. 7:458, paragraph 1 civil code). With the use of nanomedical procedures however it will become more difficult to work in compliance with this law. Nanomedicine can potentially be used for many different kinds of procedures, some of these are of a medical nature and some are non-medical (Kelly 2010). The medical procedures will all be subject to the same laws and will therefore also be subject to the rules about doctor-patient confidentiality. The non-medical procedures are

those used for scientific research and development of the research field, but herein also lies the problem. The line between what can be characterized as a medical procedure and what can be characterized as a non-medical procedure is a very fine line that is unclear on many subjects (McHale 2009). The information that is gathered about someone using a certain type of nanomedical technology can become freely available when it is done outside of a medical environment. But because the separation between the medical and non-medical field is very unclear in regards to nanomedical technology it is difficult to protect the privacy of patients. The line between these two different kinds of research will therefore have to be drawn at a certain point so that privacy and patient data can be kept safe and restricted (EGE 2007). Another problem that nanomedical procedures have in regard to the privacy or doctor-patient confidentiality is that even with distinct non-medical procedures the gathered information can still be of a sensitive or personal nature. This is because procedures using nanoparticles or nanotechnology are capable of giving much more information about a person's body than current medical or research techniques. This means that even with a procedure using nanomedicine for research ends (non-medical), the information gathered from this patient can still be a breach of that patient's privacy (Glenn & Boyce 2012). In order to make sure that the privacy and rights of people are respected the ethical thing to do is to create or adapt the current legal aspects, so that they will cover all forms of nanomedical procedures and research. The difficulty here is to find a way that protects human rights and their privacy and dignity, but does not hinder the development of the nanomedical field or the way in which specialists perform their jobs.

Discussion & Conclusion

Here at the end of all things, or at least at the end of this thesis, in find myself at a crossroads. During the course of this research I have found that despite all of the recent attention and breakthroughs that have been made in the field of nanomedicine, it has actually been around for quite some time now. It was just that the technology wasn't advanced enough up until now for a rapid nanomedical advancement (Freitas 2005). The question I ask myself is this: how is it that will all the technological marvels we have had over the last couple of decades and the tremendous increase in global cooperation, that there is still no complete understanding of a technology such as nanomedicine, that has been around since the 1950's? It is safe to say that the research I have put into this thesis has actually given me more questions than answers. And my hope is that the presentation of my findings will do the same for others who read it, because questions direct the search for answers and therefore lead to progress.

Discussion

During this research I have found that nanomedicine can have a great potential when it comes to the improvement of medicine and maybe even the improvement of the human physiology or even the human race. The use of technologies such as these will offer a great improvement to the way we run our diagnostic and therapeutic procedures in hospitals. The usage of nanoparticles to accurately map the spread of cancer or the improvement of biochips using microscopic nanosensors so that we can incorporate both detection method and a cure onto a chip the size of a grain of rice (Oberdörster 2010; Hock et al 2011). Apart from that it can also be used to achieve targeted drug delivery in precise parts of the body or used as a regenerative form of medicine, were the nanoparticles are used to stimulate the body's own defensive and healing mechanisms (Chowdhury 2010; Zarbin et al 2012). My initial thoughts on the subject were that it could be used for many goals and purposes inside the human body and also for ex vivo research. From the curing of illnesses to the strengthening of our bodies and even the further evolvement of the human race. In theory my own thoughts have been confirmed, because almost every author tells about the almost unlimited potential that nanomedicine can offer us for the medical field. In practice however there seemed to be a big difference in what kinds of promises nanomedicine holds in store for us and what is actually possible. This is a trend that I have found in almost every article or study regarding the subject. From the late 1900s up to the start of 2014, almost all the authors speak of the near limitless potential that nanomedicine can offer us in the near future. But the thoughts of those authors in in the late 1900s have as of yet not been proven right. They thought that by this time nanomedicine would have evolved to a stage where it would ban disease and cure human defects of all sorts, but the reality is that it is still mostly

in a research and testing phase. The authors of the last ten years have also been saying that nanomedicine will be the answer to all the problems of the medical field in the near future (Bawa & Johnson 2007; Costa et al 2011; Kelly 2010; Taub 2011), but I am actually pretty sceptic about this. Because however great the potential of this technology is and no matter how many improvements it can offer us, it is still a technology that needs to be researched by mankind and improved by mankind. Now don't get me wrong, I completely agree with the authors that nanomedicine offers great potential, but I don't think that it will do so in the near future. Because if there are two things that mankind excels at than it is to on the one hand to innovate and create and on the other hand to regulate and control. This is something you see in almost every field of research, but maybe even more so in the field of nanomedicine. Every discovery and innovation is paired with a certain legal aspect or ethical viewpoint that also has to be taken into account during its further development and usage (McHale 2009; Shils 2013; Spagnolo & Daloiso 2009). This is a good thing, because it allows us to regulate and control the way that progress is made and it makes sure that the progress that is made is done in the safest possible manner, with regard for human rights and dignity. This safe and responsible way of research and development is something that is necessary in a modern society such as ours, but it is also something that somewhat slows down the progress of science. Think about it for a second and think about what has been achieved in the past by scientist who were not constrained by the many rules and regulations we have today. The discovery of penicillins by Alexander Fleming, who grew them in his lab using moulds and fungi. Or the discovery of x-rays by Wilhelm Roentgen, who did not yet know about the dangers of radiation but was awarded a Nobel Prize for his work. My point here is that the advancement of science and the development of new technologies is directed in way that takes into account the many different ethical aspects that are involved and also has to be in accordance with the rules and regulations.

By also taking all these aspects of ethicality and legality into account the advancement of science and nanomedicine has been somewhat slowed down, from a roaring gallop to a steady pace. In the case of nanomedicine this maybe even be more so and even more necessary, because of the many potential risks that can also be involved with it. As described in detail in the previous chapters, nanotechnology and nanomedicine are research fields that are riddled with potential risks and negative side-effects, which can greatly harm others or our society. Some of the risks include things such as side-effects from nanoparticle residue, possible toxicological effects due to nanoparticle build-up in the human system or even the unexpected effects that can be the result of interaction between nanoparticles and the biological substances in our bodies (De Jong & Borm 2008; Linkov et al 2008; Oberdörster 2010). The existence of these risks is known, but the way to eliminate or

combat them is not. This is why the stakeholders that are involved with the nanomedical research field are looking for a way to legally insure that the safety of nanomedical trials, procedures, medicines and research can be guaranteed. The implications of this are quite substantial, because at the moment several administrations and experts in the field are looking for ways to implement nanomedicine into the existing laws or are exploring ways to create new and more specific laws and regulations that will help contain as much of the risks as possible. In my opinion this is a necessary evil in order to safely develop this quite extensive area of research even further. It may slow the research somewhat down, but it is the right thing to do and we have to do it if we want to be able to one day safely use this form of technology in our everyday lives.

Besides the legal aspects there is also a lot of discussion regarding the ethical dilemmas and problems that might be created because of the use of nanomedicine. The ethics involving a procedure or the creation of something such as nanomedicine, are in my opinion even more important than the legal aspects. Not because ethics tell us what is the right thing to do, but because ethics guide us in a way that will ensure a society that is fair and respectful for everyone involved. Thus creating a society where the benefits and risks are shared equally, so that decisions can be made more fairly. Looking at the possible ethical problems that nanomedicine may create, it is as most authors say very difficult but also very necessary to always be mindful of the ethics that are involved. Problems such as the equal spread of risks and benefits and whether or not it is ethical to treat someone with a procedure of which the entire scope of risks and side-effects isn't known (Bawa & Johnson 2007; Bennet & Naranja 2013). If our human identity can be maintained or if it will change because of the potential usages of nanomedicine. The ancient ethical question of "what does it mean to be human" is one that comes to mind (Lenk & Biller-Adorno 2007). These questions and problems will have to be addressed before nanomedicine actually becomes a part of everyday medical procedures. The biggest ethical dilemma that nanomedicine poses for me is actually not the more abstract questions about solidarity and what it means to be human, but rather the aspect of human involvement and the problem of informed consent (Resnik & Tinkle 2009). Because of the large amounts of information concerning the risks and possible long term effects that are still missing about a lot of procedures and uses it is in my opinion impossible to achieve a good form of informed consent from a patient that has to undergo such procedures. Because not only do the doctors or practitioners not know what can happen, but they are also unable to brief a patient about their procedure or to involve them in the decision making process of their treatment. For me one of the foundations of the more modern practice of medicine, is that the patients have the ability and possibility to discuss their treatment and have a say in its course. With a procedure using nanomedical

applications a lot of this will be taken away from the patients, because they cannot make informed decisions when the information isn't there. The implications of using nanomedical technologies, before they are properly researched on every aspect, can therefore lead to set back in the way that are medical system works. From a more collaborative approach to treatment planning back to a system were patients will become more dependent upon their carers again, for information regarding their treatment.

This research has been done in the timespan of roughly three quarters of a year, in that time a large amount of literature has been reviewed and processed. This time span is however way too short for a real literature review that encompasses most of the current literature. It is therefore my hope that the articles, reports and opinions that have been reviewed in this article will contribute to a more easily accessible platform regarding this subject. The problem with most of the literature I found is that it was written from one specific point of view, either a medical one, a legal one or one concerning the ethics, but almost never a combination of the three. This came as quite a surprise to me, because in the field of nanomedicine these three aspects are all in some way interdependent upon one another. The finding presented in this thesis are put together from a multitude of sources and authors, but are nevertheless still only a small part of all the literature concerning these subjects. This thesis is therefore ill suited to function as an information platform all on its own, but can be used to better understand the more specific articles and research out there. In order to really create an information platform for both the legal and the medical field it will be necessary to make a larger review, containing more different articles and even more expert opinions. In the current time span this was regrettably not possible.

My advice for any future research into the subject of the legal and ethical aspects associated with nanomedicine in patient care would therefore be to first focus on the potential ethical problems that the technology can have. Not only on a more global scale, research for equal access and distribution of benefits and risks, but mostly on a more personal and individualistic level. Researching the impact that using such procedures can have on a person's privacy or the ability that they have to make informed decisions about their treatments. This is, as I said before, for me one of the cornerstones of modern medicine and is necessary to first stabilize before one can incorporate rules, regulation and new medical procedures. Because trying to find a solution to the problems of society is best served by first finding a solution for the individual and to involve that individual in the solution for another and so on and so forth, until you are able to find a solution for the problems of society together instead of with a select few.

Summary and conclusion

As you might remember it was my aim to create a report that could function as an information platform for others who would research the same or a similar subject. In order to facilitate this process I have tried to find the answer to the following research question:

"What are the current legal and ethical aspects associated with nanomedicine in patient care?"

In the past few chapters you have seen the different findings, opinions and contributions of other authors and my own thoughts on the subjects described in detail. As you have seen nanomedicine is a complex field of research that has an overlap with many other fields of research such as nanotechnology and toxicology. Because of this overlap there seems to be no general definition of the term nanomedicine. This is because there is still no consensus about what can be defined as "nano" or whether nanomedicine is a field on its own or simply a variant on the larger field of nanotechnology. Apart from this lack of definition it can be used for a large array of procedures, ranging from diagnostic procedures to therapeutic possibilities that can be beneficial for patient care. The benefits that it can have for the field of medicine and our species is not however without risks or problems. Nanomedicine carries with it a large number or still unknown risks, ranging from potential side-effects and difficulties in finding the correct dosage, to potential risks of damage to the body due to unforeseen interaction between nanoparticles and our own biological substances. As of yet, most of these risks and potential long term effects are still unknown which makes it unclear whether nanomedical procedures will be able to be used in medical procedures. From a legal point of view these uncertainties create a certain amount of problems. As of yet there is no specific set of laws or regulations for the field of nanomedicine and it is difficult to place under one of the current laws regarding the medical field. But before the existing laws can be adapted or a new one can be created there are first a few uncertainties about nanomedicine that have to be addressed. These are the ambiguity over the classification, the manufacturing method ("golden" standard for creating the materials), the development procedure and the safety issues. Only when these four problem areas are addressed can nanomedicine be incorporated into a regulatory framework. The legal aspects associated with nanomedicine are still underdeveloped and will need to be created with regard for the ethical dilemmas as well. The ethical aspects of nanomedicine are divided into the bioethical aspects and the social ethical aspects. The bioethical aspects that have to be taken into account for nanomedicine are those concerning the protection of individuals, this includes making sure that the individual rights are respected, people still have the ability to give a free and well informed consent and the risks and benefits of the technology should be divided equally. Apart from that the information gathered with nanomedical procedures also has to

be monitored so that it will not breach the basic rights of privacy. From the social ethical standpoint the field of nanomedicine has to be monitored just as extensively. In order for nanomedicine to remain accessible to the public it must also remain in public hands up to a certain degree. Therefore it will have to be incorporated into the economic strategies of the different countries so that the necessary investments can be made. One of the larger social aspects is that of respect for the pluralistic society we have, in order to maintain this it will be necessary to watch out for the possible effects that a technology such as nanomedicine can have on the individual differences that exist around the globe. From a social viewpoint it is also important to keep a close eye on the respect for individual rights of people and to involve the individual in the decision making process to further familiarise them with the subject of nanomedicine.

A large number of both legal and ethical aspects are associated with the field of nanomedicine, but they all have one thing in common and that is that there is still a large amount of uncertainty on the subject. Whether it's about the potential risks of nanomedicine, the way that people's individual rights and privacy will be affected or how to incorporate nanomedicine into a legal framework. Much is still unclear and further studies and research are needed if nanomedicine is ever to be implemented into modern day medicine. Because it is as the founding father of nanomedicine once said:

It is in the admission of ignorance and the admission of uncertainty that there is a hope for the continuous motion of human beings in some direction that doesn't get confined or permanently blocked, as it has so many times before in various periods in the history of man.

- Richard P. Feynman-

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