Challenges of translational research in cutting edge medical technology: A case of first-in-human (FIH) trials of medical applications of nanotechnology

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Brief Summary

The translation of discoveries in basic science into safe and effective clinical applications is essential for improving health care. Unfortunately, translational research is a long, arduous and resource intense process filled with high levels of uncertainty and renown for resulting in a series of failures before succeeding in its goal. This is particularly true when cutting-edge medical technologies are translated into improved diagnostic tests or better and safer therapeutic options. The aim of this doctoral research project was to describe the challenges involved in the translational research of medical applications of nanotechnology with a particular focus on first-in-human (FIH) trials.

This exploratory research project was situated in a larger study and included in-depth qualitative interviews to gain insight into the perspectives of various stakeholders involved in planning, conducting or evaluating FIH trials in nanomedicine. Translational research is a multi-stakeholder enterprise and often requires the negotiation of various conflicting values and goals. FIH trials mark the moment in translational research when an experimental intervention is tested in human beings first time and poses the highest level of uncertainty with regard to the safety and efficacy. In-depth interviews conducted with expert stakeholders based in Europe and North America led to a greater understanding of the various challenges in translational nanomedicine and potential solutions.

The key results of this research project indicate a number of challenges in the current practices of translational research. The results are mainly focused on insights obtained from stakeholder interviews and point to issues such as (1) diverse definitions of nanomedicine and its impact on the translational research, (2) financial, ethical and regulatory challenges in the translational research, (3) inconsistent disclosure practices with regard to the 'nano' nature of investigational products in patient information sheets and informed consent forms, (4) implications of the current practices of the researchers of including patients with end-stage cancer and no effective treatment options in FIH trials on the scientific value of the early phases of the translational research and (5) factors such as public health emergencies that can accelerate decision making and mobilize resources to initiate FIH trials with investigational products despite significant uncertainty related to their safety and efficacy.

To understand all the complexities of translational research in nanomedicine, there is a need to further investigate the role of various regulatory guidelines and to define 'meaningful' public engagement in science and drug development. Both these aspects critically hinge upon scientific integrity and the public's trust in science and regulatory mechanisms. Although these topics were not investigated in this research project, our results clearly indicate the need to explore them further. We conclude that while discussing the regulation of nanotechnology, careful attention must be paid to each application on a *case-by-case* basis. We argue for the critical examination of current procedures in regulatory assessments rather than creating new and special regulations for nanomedicine. Finally, we believe that the challenges in translational nanomedicine discussed in this project are also applicable to any cutting-edge medical technology.

Thesis outline

Chapter one situates this research project within the existing scientific literature on translational research, nanomedicine and ethical issues of first-in-human (FIH) trials, identifies the knowledge gaps and defines objectives of the study. It also lists peer reviewed publications included in this doctoral thesis and outlines doctoral student's contribution to each of those manuscripts.

Chapter two elaborates on the methodological approach of the study and the experience of field work and data collection; discusses implications of the methodology on the interpretation of results in terms of strengths and weaknesses; and reflects on ways in which doctoral student's presence could have influenced the study and how the study influenced the student.

Chapter three demonstrates the diversity in the definition of nanomedicine and critically examines its impact on the funding policy, drug regulatory approvals, ethical review, patent procedures, large pharmaceutical industry, patient population and the general public.

Chapter four discusses the particulars of financial, ethical and regulatory challenges faced by stakeholders of translational nanomedicine and proposes a few solutions.

Chapter five critically examines the views of ethics committee members, investigators and trial physicians on the explicit mention of the 'nano' nature of investigational molecules in trial related documents (patient information sheets and informed consent forms) of a FIH trial.

Chapter six problematizes the current practice of enrolling patients with end-stage cancer and no treatment options in FIH trials of cancer nanomedicine. Drawing on the views and experiences shared by the investigators, physicians and ethics committee members, an alternative category of patients that could be considered for such trials is proposed.

Chapter seven looks at the circumstances which could accelerate translational research. Public health emergency of the 2014 Ebola epidemic necessitated fast track FIH vaccine and drug trials with modified trial designs in affected countries, thus raising important ethical questions regarding trial design and participant selection.

Chapter eight critically examines the clinical research guidelines issued by the Indian Council of Medical Research. Until recently, India has been a prominent hub of international drug trials though not necessarily FIH trials. This chapter problematizes the adequacy of India's clinical research guidelines to facilitate scientifically sound clinical research and to protect its human subjects.

Chapter nine focuses on an overall discussion of this PhD thesis. In addition to linking discussions related to each of the previous chapters, it reflects on limitations of the study, and elaborates implications for future research.

Chapter 1

Introduction

Priya Satalkar

Background

All countries around the globe are concerned about mounting health care costs, irrespective of their economic strength. Health care systems address the population's health care needs in three main ways. First is disease prevention, which is generally cost effective, but also challenging to implement. The second is developing sensitive and specific diagnostic tools for early detection of diseases and complications and to monitor disease progression. The third is the development, approval and availability of affordable, safe and effective drugs to cure or treat diseases and complications.

All abovementioned health care approaches rely on basic science research in multiple scientific disciplines. It has been noted that less than 10% of basic research with significant potential to improve human health and well-being is translated into clinical applications[1,2]. Inadequate and inefficient research translation is well illustrated by considering the development and licensing of a new drug, which is estimated to cost approximately $800million[3-5]. The drug development process takes 15-20 years and requires screening and testing approximately 8000 molecules/compounds to 'hit' one new effective drug. Though annual research and development costs incurred by pharmaceutical industries have grown exponentially over last decades, the number of new drugs approved each year by the US FDA has remained more or less static (average 30/year) or declined[6]. Among newly approved drugs, only 20 to 25% are actually "new", while the rest are reformulations or new combinations of drugs already approved. There is a growing concern about the huge profit margins of the pharmaceutical industry, improper drug pricing and disproportionate expenditure on marketing and advertising as compared to research and development (R&D) costs[7]. Pharmaceutical drug development has become a time consuming, resource intense and inefficient process with significant impact on health care needs of global populations (e.g., there have been only four new classes of antibiotics developed since 1960s in spite of growing concerns about microbial resistance to number of key antibiotics currently in use[8]). In

addition, despite a significant focus on R&D in cancer chemotherapy, there are few effective drugs for cancers of the lungs, ovaries and pancreas that can significantly improve treatment outcomes in patients while minimizing adverse effects[9]. It is in this context that cutting-edge biotechnology is expected to play a significant role by stimulating the development of highly sensitive diagnostic, screening and monitoring tools and targeted therapeutic options[7].

Nanotechnology: An example of cutting-edge technology

Biotechnology, nanotechnology, cognitive science, and information technology are collectively referred to as converging technology. The term converging technology implies that these four rapidly growing technologies can have synergistic applications to improve health care delivery and provide personalized medicine[10]. This research project is focused on nanotechnology and in particular its medical application. There has been a surge of funding in the field of nanotechnology[11] with a corresponding increase in basic science research and calls for heightened scrutiny and regulation[12]. Nanotechnology is expected to have a significant impact on the field of medicine. One study identified approximately 40 approved nanotechnology-based medical products (drugs and contrast agents for imaging studies) on the world market[13]. Another study identified 40 devices and 33 drugs based on nanotechnology approved globally[14]. It is important to reflect on the ethical, legal and social issues related to nanotechnology and nanomedicine while the field is evolving. This will allow for a better informed regulatory and policy framework to harness nanotechnology's potential to meet the most important population needs without compromising disadvantaged populations or the environment[15]. This doctoral research is situated in a larger project that focuses on risk benefit evaluation of nanomedicine and synthetic biology. Brief description of nanotechnology below will continue with the discussion on its specific contributions to medicine and health care.

The word 'nanotechnology' comes from the Greek word 'nanos', which means dwarf. Nano is a scale to measure particle size that is one billionth of a meter[16]. The word nanotechnology was first used by Norio Taniguchi in 1974, but many regard Richard Feynman's address in Caltech in 1959 to have ushered the era of nanotechnology[17]. The most influential definition of nanotechnology that has shaped funding decisions, policy and regulatory frameworks and patent approvals around the world was provided by the National Nanotechnology Initiative of the US[18], which states that nanotechnology is,

> …the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale.

Although nanomedicine is generally defined as the medical application of nanotechnology, there is vast diversity in definitions from various scientific and drug regulatory authorities. The impact of these definitions is discussed in chapter 3. By virtue of the nano-scale size and unique physical, chemical, optical, electric and magnetic properties, nanomedicine is expected to have a significant impact on all three approaches to health care mentioned in the opening section of this chapter. Nanomedicine can produce improved and more sensitive diagnostic tests to facilitate early disease detection [9]. It has the potential to produce improved and targeted therapeutic modalities with fewer side effects and improved efficacy[13]. It can provide the tools to continuously monitor individuals' health. It can also facilitate theranostic applications, which are approaches to produce "more specific, individualized therapies for various diseases, and to combine diagnostic and therapeutic capabilities into a single agent"[19]. Finally nanotechnology has the potential for miniaturization and increased sensitivity and is expected to significantly improve the efficiency of pharmaceutical drug development[7].

However, there are also critical voices concerned about nanotoxicity and the long-term effects of nanoparticle exposure on humans and the environment[20-22]. Concerns have been

raised about the fair and just distribution of improved diagnostic and therapeutic tools across the world, and nanotechnological advancements in high-resource countries (HRC) that could create further health inequality and disparity between HRC and low-resource countries[17]. Some scholars have also raised questions about the potential for a dual-use of nanotechnology and its possible misuse in bioterrorism[17]. Others have highlighted the possibility that nanotechnology could be used as a tool for human enhancement and its most prominent application would be in military research to create super-soldiers for combat warfare[23]. The public's perception of nanotechnology has been mixed, but so is the public's knowledge of nanotechnology. Experts have called for public engagement and participation while regulating nanotechnology[24] mainly to avoid a societal backlash as was the case of genetically modified organisms (GMO) in Europe. Even in nanomedicine, there is significant uncertainty regarding long-term toxicity of nanoparticle exposure, the validity and reliability of existing toxicological assessment tests to fully characterize nanoparticle risks, and whether patients enrolled in clinical trials of medical applications of nanotechnology are capable of providing truly informed consent given the complexity of technology involved[25].

Research in cutting-edge technology in isolation is not going to be effective for health care purposes unless systematic efforts are made to facilitate translation of those breakthroughs into concrete applications for human health. This realization has compelled many national and international scientific and regulatory bodies to focus on the translational research of any cutting-edge technology including nanotechnology [26,27].

Translational research and first-in-human trials

The Institute of Medicines' 'Crossing the Quality Chasm' report [28] divides translational research into two distinct (T1 and T2), yet inter-related phases. The first phase, T1, is typically described as translational research from the 'bench to the bedside' and involves "..transfer of new understandings of disease mechanisms gained in the laboratory into the

development of new methods for diagnosis, therapy, and prevention and their first testing in humans"[29]. Thus T1 ends with the approval of new drugs or diagnostic tests. The second phase of translational research, T2, involves the translation of interventions (proven in clinical trials) into clinical practice and eventually into health care policy. Both these phases are equally valuable to ensure provision of evidence-based health care.

However, there is another arm of translational research, which is from 'bedside to bench'. Here the challenges or limitations experienced in health care practice initiate basic science research in search of solutions[30]. This research is generally driven by the patient needs. Bedside-to-bench translational research requires that feedback from unsuccessful clinical trials is given to the bench researchers for further modification of investigational products and preclinical testing. This aspect is often ignored when investigational products are completely abandoned after failed initial clinical testing[30]. To be successful, translational research requires collaboration between basic scientists, physicians and a large number of stakeholders in spite of their conflicting and competitive interests and goals.

In bench-to-bedside translational research, most critical and highly uncertain step is first-in-human (FIH) clinical trial. This is when an investigational product is tested in humans for the first time[31]. The high degree of uncertainty is attributed to the limited validity and reliability of preclinical research,[32,33] questions concerning the appropriateness of animal models,[34] and the lack of clarity regarding the investigational product's mechanism of action.[35] The goal of FIH trials is to gather information on the drug's mechanism of action, toxicity and safety profile, and to determine a safe and tolerable dose in humans (the starting dose for clinical trials wherein the efficiency of the drug is tested).[36] The dose escalation design of FIH trials makes it highly unlikely that patients participating in such trials will receive clinically relevant therapeutic benefit, at least in the earlier cohorts using low drug doses.[37] Trial participants are likely to experience side effects and harm of various type, magnitude, and probability.[38] Some harm can be predicted from preclinical animal data.

However, data from animal models cannot always be reliably extrapolated to human beings and substantial uncertainty and ignorance persists while assessing the risks of FIH trials.[39]

The death of Jesse Gelsinger in a FIH trial of gene transfer technique for ornithine transcarbamylase deficiency in 1999 had a significant impact on the field of gene transfer.[31] This example shows the highly uncertain context in which the decision is made to start a FIH trial of a novel medical technology. It compelled scientists, clinicians, drug regulatory authorities, ethics committees and scientific review boards to undertake comprehensive and careful assessment of all the risks and uncertainties before initiating a FIH trial.

Exploring first-in-human trials in nanomedicine

Nanomedicine with inherent novel properties and potential to improve health and well-being has created many expectations in the minds of patients seeking solutions for their health concerns. The same novel properties of nanomaterials have also created fear and concerns about their long-term impact on human beings and the environment. While some stakeholders ask for a streamlined regulatory environment to harness the full potential of technology, others advocate for stricter regulation given the high level of inherent uncertainty and risk. This scenario has significant implications for translational research in nanomedicine, particularly in relation to planning and conducting FIH trials.

Though there is a large number of scientists exploring ethical issues of nanomedicine and nanotechnology, most of this literature is speculative or focused on futuristic scenarios such as human enhancement and nanorobots flowing through the body and selectively destroying cancer cells[23]. Such scenarios are striking enough to gather the public's attention and initiate an ethical debate, but they tend to further polarize public opinion.

On the other hand, there are a number of products in the clinical development pipeline that are likely to get tested in humans in the next three to five years. It is critical to understand the challenges to translate these promising nanomedicine discoveries into clinical applications

in the context of heightened hopes, fears and hype. Since translational research is a long process over many years, I focused on FIH trials that pose the highest level of uncertainty and require thorough ethical and regulatory reviews to protect human research subjects.

Translational research is a multidisciplinary enterprise and each stakeholder has their own interest. These interests could be competitive or even contradictory to the interests of other stakeholders. There is limited empirical research that assesses the knowledge, perception and views of various stakeholders engaged in nanotechnology and nanomedicine. One study examined the attitudes and knowledge of nanoscientists in Portugal about ethical issues[40]. Two ethnographic investigations examined critical decision making in a nanotechnology laboratory to understand how nanoscientists engage in ethics in day to day research environment [41,42]. Large surveys in the US and in the UK have looked at experts' and general public's knowledge and attitudes towards nanotechnology and found a relation between exposure to information and risk perception [43,44].

To the best of our knowledge, there is no other study where the perspectives of multiple stakeholders involved in FIH trials in nanomedicine have been explored empirically. To understand how diverse interests of various stakeholders are negotiated and decisions are made to initiate a FIH trial in nanomedicine, and to explore the procedure of the ethical and regulatory review of proposed trials and informing and recruiting trial participants, an empirical qualitative enquiry was used. This doctoral research project is situated in a larger research project which envisioned an interdisciplinary, multi-stakeholder risk-benefit evaluation of four concrete FIH trials in nanomedicine and synthetic biology.

Research objectives

The goal of this exploratory interdisciplinary research project (subpart of the original project) was to describe and explore challenges of translational research in medical applications of nanotechnology (this choice is explained in greater details in the next chapter on methodology) with a particular focus on FIH trials. These challenges were investigated from the point of view of stakeholders involved in translational nanomedicine. The main research questions of this study were:

1. What challenges do the stakeholders in translational nanomedicine face while planning or conducting a FIH trial?
2. What are the ethical challenges in planning or conducting FIH trials in nanomedicine?
3. What factors or circumstances could facilitate translational research, in particular FIH trials?
4. How do the ethics committee members review proposals of FIH trials when significant uncertainty and ignorance exists in respect to risk assessment?

Contribution to project related publications.

Prof. Elger wrote the original project within which this doctoral research project is situated and she also received the funding. I conducted 46 interviews, transcribed and analyzed them. I received some inputs in data analysis from Dr Shaw. There are six publications included in this thesis. In each one of them I took the lead, thought of an idea, conceptualized the structure, and wrote the first draft. I received feedback from Prof. Elger, Dr. Shaw and from Prof. Hunziker (for one paper). Dr. Shaw reviewed each manuscript before submission as a native speaker.

Following peer reviewed publications are included in this thesis:

1. Satalkar P, Elger BS, and Shaw D. (2016) Stakeholder views on participant selection for first-in-human trials in cancer nanomedicine. *Current Oncology*. 23(6): e530-e537.
2. Satalkar P, Elger BS and Shaw D. (2016) Defining nano, nanotechnology and nanomedicine: Why should it matter? *Science and Engineering Ethics.* 22(5):1255-1276.
3. Satalkar P, Elger BS, Hunziker P, and Shaw D. (2016) Challenges of clinical translation in nanomedicine. A qualitative study. *Nanomedicine: Nanotechnology, Biology and Medicine.* 12(4):893-890.
4. Satalkar P, Elger BS, and Shaw D. (2016) Naming it "Nano": Stakeholders' views on use of "nano" terminology in informed consent forms of first in human trials in nanomedicine. *Nanomedicine*. 11(8):933-940.
5. Satalkar P, Elger BS, and Shaw D. (2015) Prioritizing Healthcare Workers for Ebola Treatment: Treating Those at Greatest Risk to Confer Greatest Benefit. *Developing World Bioethics.* 15(2): 59-67.
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Chapter 2

Methodology

Priya Satalkar

Outline

This PhD project is part of a larger research project funded by the Swiss National Science Foundation, a grant obtained by Prof. Bernice Elger. In this chapter, I will describe the methodological approach of my doctoral research, elaborate on my experience of field work and data collection, and outline the methodological limitations that need to be kept in mind while interpreting the findings of this study. This chapter is intentionally written in first person singular (i.e. I format) as it mainly describes on the process of field work and data collection as part of this research project and involves self-reflection as a researcher.

Original research project

The focus of the original research project was on ethical issues of cutting edge medical technology, envisioned as an interdisciplinary research project in empirical ethics to understand the procedure of risk/benefit evaluation of first-in-human (FIH) trials in synthetic biology and nanomedicine. It was designed as a mixed method study, conducted by two doctoral students, each looking at one medical technology with concrete examples of FIH trials, either ongoing or those at the stage of planning.

Defining my doctoral research project

Though there is a significant surge in the academic literature on ethics of nanomedicine, nanotechnology, and synthetic biology, we realized that there was limited empirical investigation of the ethical issues. We were interested in understanding the ethical issues faced by stakeholders involved in translational research and to gather their views on possible solutions. Nanomedicine, as a scientific field, is further along the translational pathway as compared to synthetic biology, which is still mainly at the stage of preclinical research. My linguistic limitations to communicate in German made it logistically convenient that I would interview expert stakeholders in both translational nanomedicine and synthetic biology while my German speaking colleague would do surveys with patients at a local hospital and we would work together on data analysis and summarizing results on both data sets.

To narrow the scope of my project while keeping in line with the original project, I decided to focus on FIH trials, which pose the highest level of uncertainty during translational research. In-depth interviews facilitated by a semi-structured interview guide allowed me to explore the views and experiences of stakeholders while giving them the opportunity to describe their rationale, arguments, and concerns.

The original plan for me was to conduct a total of 40 in-depth interviews. Half of these interviews would be with the stakeholders based in Switzerland (since the project was funded by the Swiss National Science Foundation) and the remaining 20 could be situated anywhere in the world. I was to interview 20 scientists who had either conducted or were planning to conduct FIH trials in nanomedicine or synthetic biology and 20 ethics committee members who had evaluated such FIH trials, thus having equal representation of these two stakeholders in the study sample.

An extensive literature review undertaken in the first year of my PhD helped clarify a number of aspects of my research project. My first realization was that translational research and clinical trials are a multidisciplinary enterprise and a category of "scientist" is too restrictive. To gain a complete picture of the challenges of conducting FIH trials, I decided to elicit the views of different stakeholders who are *integral* in translational research and not necessarily just scientists working on nanotechnology. Second, conducting the literature review helped me shift the focus of my research question from risk/benefit evaluation to general challenges of taking a promising medical application from "the bench" and successful animal studies to "the bedside" and clinical practice. Third, to accommodate diverse categories of stakeholders in translational research, my interview guide had to be comprehensive yet flexible so that depending on the profile and exact role a potential respondent plays in translational research, I could smoothly transition to questions that were relevant to that respondent. Finally, the review reinforced our original assessment that nanomedicine, as a field, has matured more than synthetic biology and hence it would be most

relevant for me to solely focus on the medical applications of nanotechnology rather than it and synthetic biology.

Experience of field work and data collection

In the first year of my PhD, apart from undertaking periodic literature searches, refining and pilot testing my interview guide, and getting necessary ethics approvals, I carried out "participant observation" at four key nanomedicine conferences and meetings in Switzerland and France. The focus of this participant observation was to understand the current state of nanomedicine along the translational research pathway, assess who has conducted or is planning to conduct FIH trials and to introduce myself to these professionals. I actively participated in scientific sessions as well as evening socializing events at these conferences where I observed conference delegates interact with one another and openly discuss challenges they faced. These meetings and conferences also had heated debates on certain topics, such as defining nanomedicine, nanocharacterization capacity and the state of translational research in the US as compared to Europe. I took extensive notes of these observations and insights but did not use this data in my research writing for two reasons. First, I did not know what kind of ethical approval one needs to carry out participant observation at a conference in which one officially participates (e.g. is registered and presents a research paper). Second, I was unsure how reliable was information obtained at informal evening talks, over a glass of wine, where most delegates were relaxed and more open to share their thoughts. However, participation in these conferences improved my familiarity with the field of nanomedicine and provided me with a new identity conferred by the conference participants –"the girl studying ethics of FIH nano trials."

Still, it was quite challenging to get the stakeholders to agree to do an interview with me. They were extremely busy and their priority was to find solutions to their challenges by collaborating with others and not spending 30 minutes with a doctoral student who wanted to understand those very same challenges. Some were concerned about talking to a PhD student

in ethics about their technology platform and FIH trial, worried that I might share their sensitive research information unknowingly while interviewing others (perhaps their competitors). A few of them directly and bluntly asked me what I would give them in return for the time they would spend talking to me. A couple of them told me the hourly fees they charge as consultants and asked if I could afford that kind of money. A few wanted me to connect them with particular hospitals in India in return for an interview. At some point in time, I realized that delegates were avoiding me at these conferences; they were particularly reluctant to make eye contact and some refused to recognize me or acknowledge that we had met and talked at another conference, where they had agreed to do an interview with me.

But there were also a few who took great interest in my research, personally introduced me to others that they thought could be interesting for me to talk to, wrote emails introducing me to their colleagues and encouraged me to keep trying, especially when I felt defeated after having failed to recruit any respondents in the first 13 months of the study. A few experts confessed that they needed to keep talking about their ambitious FIH trials at such conferences as if they were going to take place in near future to receive the attention of venture capitalists and funding agencies. However, in reality, they were far from such a possibility and hence could not do an interview with me as they had nothing to share with me. The stakeholders affiliated with universities and small and medium size enterprises (SMEs) were more willing to talk to me and were interested in knowing more about my project while those from the large pharmaceutical industry were quite skeptical of me. If I introduced myself as a doctoral student in ethics, I could immediately notice the change in their interaction with me, taking on a more cautious approach. They all wanted to know my professional background before talking to me. When I disclosed that I was trained in medicine before diversifying into social science and ethics, I gained some credibility in their eyes. I finally started introducing myself as a physician and a social scientist working on challenges of translational research in nanomedicine and dropped the word “ethics” from my initial

interactions with potential respondents, even though my business card clearly stated my affiliation with the Institute for Biomedical Ethics.

Apart from making personal contact in conferences, I continued to write emails to experts in nanomedicine and requesting an interview from them. A senior expert from Switzerland told me that most of these experts receive hundreds of emails each day and hence my email being one of them is unlikely to catch their attention or fuel their curiosity about my research. He encouraged me to write hand written letters and mail those. Since it was already Christmas of 2013, I decided to combine my hand written notes with Christmas cards and sent out 60 letters to potential respondents. Five of my respondents later admitted that my letter finally compelled them to do an interview with me.

Methodology

The details of methodology such as study population, interview guide, interviews, transcriptions and qualitative data analysis have been discussed in chapters three, four, five and six. These chapters include manuscripts based on the empirical data from this research project which have either been published or are submitted to journals.

In following pages, I will reflect on the strengths and weaknesses of the methodological approach of my doctoral research while paying attention to ways in which my presence as a researcher with my personality, training, experience, and opinions could have influenced the research. Additionally, I note how the research influenced my views and opinions about the ethical challenges in translational nanomedicine.

Methodological limitations

My decision to include a broad range of stakeholders in my study population proved to be a double edged sword. It allowed me to gather views and experience from different angles but it also significantly limited the generalizability of my findings. Drug development and licensing processes as well as ethics review is highly political and influenced by each country's drug regulatory environment and ethical guidelines. It became almost impossible for me to draw

any conclusions in regards to specifics of drug regulatory procedures or ethics review because my 46 interview partners were spread across 13 countries and some countries were represented by only one respondent. I was uncomfortable to draw conclusions based on views and experience shared by one respondent as if it was representative of the reality of that country even though only a few FIH nanomedicine trials had taken place in that country often initiated by that same respondent.

Another difficulty I experienced was to interview ethics committee (EC) members who had reviewed FIH trials. Contrary to my expectations, EC members were the most difficult category of respondents to recruit. My data set has only six ethics experts, two of whom are members of National Ethics Commissions, serving advisory rather than reviewer roles. The other four who worked as EC members claimed to have no experience in evaluating FIH nanomedicine trials. In fact only two of the four stated that they had ever evaluated any FIH trial. Taking a closer look at their work load, it became clear that the majority of trials they evaluate are doctoral theses, social and behavioral research, health systems research, as well as phase II and III clinical trials. FIH and phase I trials in particular are a miniscule amount of the total number of trials these committees review. Even in Switzerland, my efforts to approach EC members for an interview did not materialize since most of them replied back saying, “We have not evaluated FIH trials in nanomedicine and hence cannot do an interview.” This scenario correlates with the fact that in general, very few FIH trials in nanomedicine have taken place in Europe, and the US remains on the forefront of conducting such trials. Unfortunately, I did not have access to IRB members in the US. I would definitely like to explore this possibility in the future.

Self-selection bias cannot be completely ruled out in this study since those who agreed to be interviewed for this project probably had different views and a greater interest in the topic than stakeholders that were not interviewed. It is not possible to assess how different

these views could be from those who did not want to be interviewed. Outright refusals were rare; often stakeholders simply did not respond back to my repeated requests for an interview.

I initially feared that respondents would provide me with answers that they thought a PhD student in bioethics would like to hear. However, during the course of these interviews, I realized that the stakeholders were honest and open about their views and willing to explain to me the line of reasoning behind their beliefs. They also enjoyed being challenged on some of their ideas. One of the reasons for this could be that most of these stakeholders were experts in their field and had no reason or incentive to please a doctoral student, and instead saw the interview as an opportunity to engage in a scientific and ethical discussion and to exchange ideas and arguments. There were a couple of respondents who tried to influence and challenge my views during the course of the interview, leading to some serious debates.

I believe the insights obtained from this exploratory research project are still valuable, especially for developing a more structured, international study using both qualitative and quantitative methodology for each category of stakeholder. It would be worthwhile to survey drug regulatory authorities or ECs from select countries to compare contexts and understand the magnitude of specific challenges. Additional interviews with these stakeholders could assist in exploring the nuances of those challenges and potential solutions to them.

Personal reflections

At every stage of qualitative research (e.g. data collection, analysis), the researcher must be aware of how his/her presence in the 'field' could influence the research and how the research could influence him/her in return. Above, I elaborated on how my presence might have influenced the research. Here I share reflections on how the research influenced me.

At the beginning of the project, I thought that nanotechnology and its medical applications raise new ethical questions and therefore FIH trials in nanomedicine should have a special status. During the course of research this initial belief underwent a significant shift. I still believe that nanotechnology, by its very nature, raises some interesting questions due to

the significant uncertainty in long term risks and risk assessment. However, I do not believe that there is any need to create a sub-discipline of nanoethics or special departments to evaluate only nanomedicine trials. One reason against creating special departments is that with converging medical technologies, dividing a drug or device based on underlying technological platform is going to be challenging. I rather believe that we need to go back to the basics of evaluating any FIH trial and pay critical attention to all procedures involved, particularly to the blind spots during drug regulatory or ethical review process. I have elaborated this point further in chapter nine on discussion.

Medical science in general focuses on empirical evidence and has a strong positivist approach. However, I was surprised to learn how many decisions in clinical research, risk assessment, drug development, and ethics review are based on intuition, trust, and the belief that everyone involved is honest and has a strong notion of research integrity. Repeated reference to trust in these interviews made me curious about the role trust plays in scientific research. More specifically, I am curious to understand threats to trust in the highly competitive drug development industry and ways to nurture and safeguard trust in science and drug development. I do not dwell on the theme of trust during my doctoral research, but I am interested in exploring it further as a next step of my academic career.

Chapter 3

Defining nano, nanotechnology and nanomedicine: Why should it matter?

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Abstract

Nanotechnology, which involves manipulation of matter on a ‘nano’ scale, is considered to be a key enabling technology. Medical applications of nanotechnology (commonly known as nanomedicine) are expected to significantly improve disease diagnostic and therapeutic modalities and subsequently reduce health care costs. However, there is no consensus on the definition of nanotechnology or nanomedicine, and this stems from the underlying debate on defining ‘nano’. This paper aims to present the diversity in the definition of nanomedicine and its impact on the translation of basic science research in nanotechnology into clinical applications. We present the insights obtained from exploratory qualitative interviews with 46 stakeholders involved in translational nanomedicine from Europe and North America. The definition of nanomedicine has implications for many aspects of translational research including: fund allocation, patents, drug regulatory review processes and approvals, ethical review processes, clinical trials and public acceptance. Given the interdisciplinary nature of the field and common interest in developing effective clinical applications, it is important to have honest and transparent communication about nanomedicine, its benefits and potential harm. A clear and consistent definition of nanomedicine would significantly facilitate trust among various stakeholders including the general public while minimizing the risk of miscommunication and undue fear of nanotechnology and nanomedicine.

Keywords

Nanotechnology, nanomedicine, definition, ethics, qualitative research, stakeholders

Introduction

The use of nanotechnology in medicine has the potential to significantly improve human health and well-being due to highly accurate and sensitive diagnostic tests (Ferrari et al. 2009), targeted therapeutic interventions (Duncan and Gaspar 2011)and theranostic applications that have a combined approach to diagnose and treat a disease using the same intervention (Lammers et al. 2011). Nanotechnology contributes to early disease detection, better treatment outcomes, and reduced health care expenditures. The interdisciplinary field of nanotechnology and nanomedicine has gained considerable attention from academia, the pharmaceutical industry, various national and international funding and regulatory agencies and the general public (Kostarelos 2006; Wagner et al. 2006; Bawa et al. 2005; Pidgeon and Rogers-Hayden 2007; Scheufele et al. 2009), and has made significant progress along the translational pathway in the last 15 years (Etheridge et al. 2013).

Nanotechnology has also raised a number of questions related to risk assessment, risk minimization (Hogle 2012), human and environmental toxicity (Ramachandran et al. 2012), and cost and fair access to the improved interventions across societies (Allhoff 2009). There has also been tremendous pressure to accelerate the translation of basic nanotechnological research into bedside clinical applications in medicine (Kola and Landis 2004). However, a high level of uncertainty about potential risks and benefits of nanoparticles and nanomedicines creates significant hurdles along this translational pathway (Lenk and Biller-Andorno 2007; Resnik and Tinkle 2007). Particularly interesting in this regard are ‘first-in-human’ (FIH) trials of medical applications of nanotechnology, as they pose the highest level of uncertainty in all clinical research (Kimmelman and London 2011).

The goal of our research project was to document the various challenges and ethical hurdles faced by stakeholders involved in the process of planning, reviewing and conducting FIH trials in nanomedicine. In this paper, we discuss diversity in the definition of nanomedicine. We begin with the definitions of nanotechnology and nanomedicine proposed

by international scientific bodies and key drug regulatory authorities. Next, we describe and discuss definitions provided by stakeholders who were interviewed in our study as compared to official definitions. Finally, we highlight concerns that arise due to the variety in definitions used by the stakeholders on ethical and regulatory review process of FIH trials in nanomedicine.

Methodology

We used exploratory qualitative research methods to gather insights from various stakeholders involved in translational nanomedicine. In-depth interviews were considered valuable and appropriate for this exploratory research since there are only a handful of empirical studies that investigated issues in translational research in nanomedicine.

Study population

Stakeholders in translational nanomedicine for the purpose of this study are scientists affiliated with universities, small and medium size enterprises (SMEs) and large pharmaceutical industry, members of national ethics advisory committees and institutional ethics committees (EC), physicians, representatives of the drug regulatory authorities, patient advocacy group, clinical research organizations and venture capital groups based in Europe and North America.

Study instrument

Based on available literature on this topic, we developed a list of open-ended interview questions to guide and facilitate interviews with the aforementioned stakeholders. The interview guide was pilot tested with fellow colleagues (a doctoral and a post-doctoral researcher with experience in qualitative research at the institute) and an expert in biotechnology ethics from the US to assess the clarity and validity of the questions. These pilot interviews were excluded from the final data set of 46 interviews. The interview guide allowed for a structured enquiry, but also provided interviewees with the necessary opportunity to elaborate on issues that they deemed critical. The interview guide was

approved by the ethics commission of Basel Stadt and Basel Land (Ethikkommission Beider Basel EKBB) in January 2013. This commission is now called the ethics commission of North-west and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ).

Sample

The interviewed experts and the stakeholders were identified through publications, university affiliations, contacts made at key scientific conferences on nanomedicine and personal and professional networks. Drug development is regulated by national(US FDA) or regional (European Medicines Agency) drug regulatory authorities, so we expected researchers planning or conducting FIH trials in nanomedicine to face distinct challenges depending on the regulatory environment in their country or the country where they planned to conduct a trial. We used a purposive sampling technique to include maximum variation in terms of the respondents' experiences, professional backgrounds and affiliations, and geographic location. We included stakeholders with views in line with the dominant discourse and those who challenge the dominant views (Devers and Frenkel 2000; Kenen et al. 2004). This approach allowed us to explore challenges in planning, conducting and reviewing FIH trials in nanomedicine from the perspectives of various stakeholders working in multiple countries. It also facilitated a reflection on the interdisciplinary nature of nanomedicine since respondents had varied professional backgrounds, roles and responsibilities that could be explored in depth. Recruitment was further facilitated by the use of a snowball sampling technique until we reached theoretical saturation, the moment during data collection when researchers realize that no new themes are emerging (Bowen 2008). For example, in our investigation of the definition of nanomedicine as described by the stakeholders, we continued to interview respondents till the point where no new aspects related to the definitions were described. The theoretical saturation was reached at various points for different research questions depending on the diversity of opinions, stakeholder heterogeneity and scope of debate on the topic.

Informed consent

The lead author of this manuscript (P.S.) conducted all 46 interviews (in person or via telephone or a Skype call) in English from October 2013 till November 2014. Oral informed consent was obtained from each respondent at the beginning of an interview, which also included permission to record the interview. All interviews were recorded on a hand held audio device except one for which the researcher was asked not to record the conversation, but to take hand-written notes. The respondents were informed about how their anonymity and confidentiality would be ensured. We removed all respondent identifiers such as name, affiliation, country and the details of the products they were developing to minimize identification. Respondents were also told that they could choose to not answer particular questions if they felt uncomfortable and that they could ask for audio recording to be stopped for particular sections of the interviews. The same procedure was used to obtain informed consent and permission for audio recording for the interviews conducted on the telephone or via a Skype call. This approach was essential to build a trusting relationship with the respondents since many were concerned about sharing sensitive and proprietary information of early clinical trials of their investigatory products with a social science researcher. Their concerns were also linked to the fact that the field of nanomedicine is comparatively small, yet specialized, and has a very close-knit scientific community.

Interviews and transcription

The interviews lasted between 20 minutes and about an hour depending on the respondent's availability and their interest in sharing their experience; the average interview was 50 minutes. Eighteen interviews were conducted in person, two respondents sent their answers to list of our questions while the remaining 26 were carried out either via the telephone or a Skype call since travel to different countries in Europe and North America was not possible due to the time and money involved. We were aware that interviewing in person compared to on the phone or Skype would impact the quality of the data. It is generally easier to develop

rapport with a respondent when interviewing in person compared to a phone conversation. We discuss this in more detail in the section on study limitations. P.S. with assistance from four team members (data assistants who had signed confidentiality agreements) transcribed all the interviews in full. P.S. checked all 46 interviews for accuracy against the audio recordings. As per our agreement with the respondents, we sent the transcript of each interview to the respondent to verify the accuracy of the content since some interviews (at least in part) were highly technical. Respondents were also encouraged to provide any additional thoughts they had when reviewing their transcript or thoughts that had arisen after the interview. We received feedback from only 13 respondents. A total of 17 respondents were re-contacted in person at a conference and told P.S. that they had briefly reviewed their transcripts but had been unwilling to go through all 20-30 pages and had assumed the transcripts were accurate. The remaining 16 transcripts were assumed to be correct and acceptable to the respondents.

Data analysis

The transcripts of all interviews formed the basic data for this research. The transcripts were read repeatedly to have a thorough understanding of the data. P.S. coded all interviews using qualitative data analysis software (MAXQDA, edition 11.0.2 licensed by the University of Basel) using deductive coding methods. The research questions guided the deductive data coding. The codes were built into subthemes and themes and compared across all respondents. A second author (DS) conducted a manual data analysis using the same deductive coding and the codes and themes were compared between the two approaches (software assisted vs manual). Similarity and differences in coding were discussed amongst the researchers who are also authors of this manuscript until a consensus was reached.

In the sections that follow, we first describe the characteristics of our respondents followed by key official definitions of nanotechnology and nanomedicine. Then we present the definitions of nanomedicine provided by our respondents during interviews and compare them with the official definitions. Finally we discuss the influence of this diversity in the

definition of nanomedicine on the regulatory and ethical review process of FIH trials in nanomedicine.

Results

Respondent profiles

A total of 21 of 46 respondents were based in Switzerland, while the remaining 25 worked in Germany, The Netherlands, the United Kingdom, Spain, Portugal, Denmark, Norway, Austria, Hungary, Israel, Canada and the US. Almost half of our respondents (20/46) described themselves as academics or scientists affiliated with a university or research institution. Respondents had diverse disciplinary backgrounds such as medicine, molecular biology, biochemistry, material science, physics, toxicology, pharmaceutical science and organic chemistry. Eight respondents represented SMEs, which play a crucial role in early translational research and particularly in obtaining a 'proof of concept' in man. SMEs are university spin-offs, often headed by academics who start a company and are funded by governmental seed grants and/or investment by venture capitalists. Eight of our respondents represented large pharmaceutical companies either as researchers, clinical research managers, consultants or regulatory affairs experts. Six respondents brought in expertise in ethics either as members of EC or institutional review boards (IRB) or being the members of national and international advisory commissions on translational research. Two respondents were affiliated with drug regulatory authorities. We also included one representative each from a venture capitalist group and a patient advocacy organization. Many of our respondents had dual roles or experiences at least during some part of their professional career. A large number of academic scientists also supported SMEs as members of their advisory boards. The diversity of disciplinary backgrounds, geographic locations and professional roles helped us to gather views and experiences across a broad range of topics and issues, which was the goal of our exploratory qualitative research.

Official definitions of Nanotechnology and Nanomedicine

National and international scientific bodies' definitions

To understand the evolution of definitions of nanotechnology and nanomedicine, it is necessary to start with publically funded research programs in this field in the US as well as in Europe. The National Nanotechnology Initiative (NNI) was launched, in 2001, in the US which led to significant funding in the field and the development of 'centers of excellence' in nanomedicine across the US. The NNI defines nanotechnology and nanomedicine as follows:

> Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale. Nanomedicine is the application of nanotechnology to medicine (National Science and Technology Council 2014).

In contrast, the European Science Foundation (ESF) defines nanomedicine as "the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body" and further highlights five key disciplines of nanomedicine: analytical tools; nanoimaging; nanomaterials and nanodevices; novel therapeutics and drug delivery systems; and clinical, regulatory, and toxicological issues (European Science Foundation 2004).

Finally, the European Technology Platform on Nanomedicines (ETPN) defines nanomedicine as "the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale. Nanomedicine has potential impact on the prevention, early and reliable diagnosis and treatment of diseases" (European Technology Platform on Nanomedicine – Nanotechnology for Health 2005).

The examples above demonstrate the diversity in nanotechnology and nanomedicine definitions. The European Science Foundation's definition focuses on broad aspects and components of nanomedicine, but does not elaborate on nanotechnology per se. However, the National Nanotechnology Initiative emphasizes the defining character of nanotechnology and refers to nanomedicine as the application of nanotechnology in medicine. This definition is the only one among the three mentioned above that defines nanoscale in terms of size dimension, i.e. from 1-100 nanometers. The definition of nanoscale is the starting point of the differences in size-based definitions of nano, nanomaterials and nanomedicine as we describe further in our results.

Drug regulatory authorities' definition

Drug regulatory authorities are closely involved with the development, research and licensing of diagnostic and therapeutic products that harness nanotechnology. We also examined the definitions provided by key drug regulatory authorities representing the geographic distribution of our respondents. The US Food and Drug Administration's (FDA) recently finalized 'guidance for industry regarding FDA regulated products involving applications of nanotechnology' highlighted two points to consider while regulating a product based on nanotechnology.

1. Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1nm to 100nm); and

2. Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000nm).

It must be noted that these guidelines also state that the recommendations are non-binding (US Food and Drug Administration 2014).

The European Medicines Agency (EMA) (2006) defines nanomedicine as "the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometer scale". In the same document, the EMA describes nanometer scale as ranging from atomic levels of 0.2nm-100nm.

In its application form for investigational medicinal products (IMPs), Swissmedic, the authority regulating medical products in Switzerland, requires investigators to elaborate and specify whether the IMP contains nanoparticles with at least one dimension in the nanoscale (1-1000nm) and whether the IMP has a function and/or mode of action based on nanotechnology characteristics either in the active substance or adjuvant. Swissmedic's focus is clearly on size as well as function or mode of action, thus making it more specific than other definitions.

Stakeholder definitions

Our respondents were encouraged to define nanomedicine in terms of properties that they believed were essential. They were all aware of the various definitions provided by multiple scientific bodies and authorities and many of the respondents were closely involved in the debates surrounding nano-nomenclature in general and defining nanomedicine, in particular. Below we present definitions provided by our stakeholders under various themes.

<u>Based on size</u>

Material with at least one dimension in the nano scale has been the key property of nanotechnology and this is reflected in the definitions of nanomedicine. But there is an ongoing debate about defining the scale that should be limited as the nanoscale. Below are some of the responses from our respondents highlighting this tension.

> Everything that is in the range of one to 100nm is nanotechnology and when you apply it in medicine it is called nanomedicine. A lot of people don't differentiate anymore

between molecular medicine and nanomedicine. We have [had] molecular medicine for a long time. **R6**

There are many definitions. One says up to 100nm, they don't give you a lower limit. Other says up to 1000nm. The definition, which is applied in politics in Germany, no I am sorry in the EU, is between one and 100nm. **R14**

However, there were also voices that were critical of a size-based definition as described below.

There is no really good definition to be honest and there are several ones. I tend to define nanomedicine as something larger than antibodies, but that is my personal one. Indeed, anything defined only by size is flawed. If you define it [nanomedicine] as up to 1000nm, what happens to a product that is 1001nm? Drugs don't fit nicely in a size dimension. This is not a step function, rather a linear function. Any attempts to spend more time on definition of nanomedicine to be honest are futile. **R10**

Based on the properties of the material

Most definitions provided by our respondents centered on the fundamental properties of the material under investigation. They attributed various properties that should be considered while defining nanomedicines as can be seen below.

Physical chemical properties

Nanomedicine is the use of nanoparticles to elicit a therapeutic response that would not be efficacious in the absence of nanoparticles. Nanomedicine is something that is beneficial because of inherent nature of nanoparticle and not just because they are very small. It is the inherent nature of nanoparticle that enhances or enables a high therapeutic efficacy, which we will not have otherwise. **R11**

However, a few respondents also questioned the importance given to the properties of nanomaterials and their uniqueness, arguing that there are no longer any unpredictable

properties owing to the advances in tools and characterization techniques. They argued that it is fully possible to predict the behavior of nanoparticles in biological systems.

> It [nanomaterials definition] is just the size definition merely and there are no unpredictable properties. They are all predictable. They were not predictable may be 10 years ago but they are now. **R10**

Organic/inorganic

Our respondents repeatedly discussed the chemical composition of nanoparticles used in medical applications mainly in terms of an organic or inorganic nature. This formed the foundation for discussion on nano-toxicity and the risks associated with the accumulation of nanoparticles in human body.

> I think, first we have to separate between organic and inorganic nanoparticles. Why? Organic nanoparticles are all these liposomes and micelles. They are well known, well used. And there is the nano in size only. They are generally below 100nm if you go by EU definition. But if you go to inorganic nanoparticles, we change their physical, chemical, magnetic, electric and optical properties. And from a scientific point of view, if you get a size where you change these properties, only then you can speak about nanoparticles. For example, in iron oxide particles, this happens below 20nm, above this size, they have same property as bulk iron oxide. And this size at which material shows changed properties is different for different materials. **R15**

Ability to be metabolized

> When we talk about nanoparticles, we need to remember there are different classes of nanoparticles. Iron oxide nanoparticles have a solid core meaning they are really solid, but when you speak about albumin, it is a bit different. It is a polymer; it is a biopolymer that you already have in your body. The truth is, we need to define [the] classes where we put our nanoparticles and also consider whether they can be

> metabolized by the body or not. If it takes a long time to metabolize, you need to know how long it will take, where in body will these particles be stored? **R19**

A large number of respondents made a clear distinction between organic and inorganic nanomaterials and more concerns were raised about inorganic nanoparticles that the human body is not exposed to in its physiological function due to their interaction with biological systems and metabolism. Respondents were troubled by the prospect of using carbon nanotubes as a drug-delivery method due to their similarity to the micro-needle structure of asbestos and their potential to cause cancer.

> I saw so many talks on carbon nanotubes being used for drug delivery. And the starting point of that, they are toxic. So you are wasting your time unless you are just doing basic research to see what kind of toxicity you are going to see. And then to use those to transport drugs across blood brain barrier it's even more ridiculous. And then the EU putting in a billion dollars for carbon nanotube research for medicine is beyond ridiculous! So I don't know what is going on, anymore. It's crazy! **R31**

Another respondent could see very limited potential for carbon nanotubes as a method for drug delivery, but anticipated significant regulatory hurdles as described below.

> I would never use carbon nanotubes as [a] drug-delivery method because it is not biodegradable, the body does not know that structure. What will happen? These materials themselves... it would not be approved by the EMA or by the FDA. Very simple! Maybe if you could demonstrate that with a nanotube a specific cancer can be cured, you have a big step in favor, superior for instance to liposomes. Maybe in cancer, because in cancer there is a lot allowed. It is maybe better to survive for some years and have a toxic substance in your body than die too early. So you could see an application for such systems, but still I would think you would have a lot of trouble at the regulatory level **R24**.

Some respondents countered that not all inorganic nanoparticles are dangerous as the human body is used to handling and metabolizing these particles. This was particularly discussed in regard to iron complexes, which have been used to treat anemia successfully.

Pharmacodynamic properties

Pharmaceutical scientists emphasized the interaction of nanosize particles with pharmacokinetics and pharmacodynamics. Their definition of nanomedicines centered on the pharmaceutical goal to achieve a higher concentration of active drug at a desired site by improving absorption or prolonging half-life. This approach could lead to a reduction in a required dose, and thus associated side effects as well as a reduction in the cost of treating a disease.

> I consider nanoparticles as a vehicle for drug delivery. When you incorporate your drug in a nanostructure, it changes its solubility, physical and chemical stability, and its interaction with the biological systems due to presence of nanostructure or a nanocarrier. For me that is changing [the] properties of a drug. Usually, per definition nano means below 100nm because below this size you have different properties of material. But, from the pharmaceutical perspective, reducing the size of a drug from micrometers to 400 or 500nm makes a significant change in the performance of a drug. Why? Because this drug due to its reduced size will dissolve faster, more drug will get absorbed in the intestine. So just by reducing the size of particles and increasing the surface area, you will have higher absorption of the drug. If that happens at 400nm, who cares? If you are increasing the bioavailability of a drug by reducing the size to 400nm, it is still nano. It is important for the scientist to think- what does nano contribute to performance of your drug? **R41**

Ability to be engineered and complex multimodular assembly

Some of our respondents specifically focused on the engineered aspects of a product or the manipulation of the material as essential to be qualified as a nanoproduct.

> While defining nanomedicine, one thing is size, you are speaking about 1-1000 nm. I would say if you have a macromolecule, or a molecular assembly where you can put different targets, different carrier molecules and you can incorporate different active compounds inside this structure, you can make an active compound reach the target better, or you can improve the solubility of a compound which was previously insoluble. For me, nanomedicine has this complex multi-modular assembly. **R25**
>
> Nanomedicine needs to be defined on case-by-case basis. If you take monoclonal antibodies, they are certainly in that size range, but I won't call then nanomedicine. For me, nanotechnology also has engineered component to it. **R39**

Sub-classes of nanoparticles

Some respondents stated that they were not concerned about the definition of nanomedicine, but instead claimed that it is important to refine the sub-classification of these nanoparticles. They argued that as the field of nanomedicine and nanocharacterization evolves, it has to reflect on the classification of various nanoparticles rather than making blanket statements about the biodegradability and composition of nano materials. These respondents argued for the need to assess each new product with nanotechnology on a *case-by-case basis* till we have sufficient knowledge and experience with different classes of particles and over a long period of time.

> Definition per se, I don't have any problem, but I think it is time to start generating sub-categories, the binning process [classifying, putting it in different bins or categories] I mentioned to you before. Definition of a molecule is equally broad, but we talk about small molecules, polymers, micro molecules, peptides, so on and so forth. **R13**

Based on size and properties

A few respondents highlighted the importance of considering both size and properties when assessing nanoparticles, since these two functions are often interdependent.

> There might be an aspect of size in definition of nanomedicine somewhere during manufacturing process or in the end product. So size is important, but it is not exclusive. I think what is much more important is to characterize such drugs or particles and their behavior in biological systems because these products behave very differently than classic molecularly dispersed products in terms of pharmacokinetics, half-life and eventual elimination from the body. **R32**

Other respondents stressed the need of mimicking naturally occurring molecules in the body, which are at the nanoscale, with the goal of enhancing drug delivery methods.

> The way that you really learn about how to deliver a drug in the body is not by collaborating with anybody who is using gold nanoparticles or polymers or dendrimers or any of this other stuff, it is to see what nature does. So the way nature delivers some of its hydrophobic materials like cholesterol, which actually forms a crystal, is to turn it into more amorphous material called cholesteryl ester or cholesteryl oleate and form nanoparticles which are called low density lipoprotein (LDL) molecules. They are 25 nm and if you want to deliver something to cancers, cancers don't eat gold. They don't eat plastics, calcium, and phosphate. What they eat is LDL particles. **R7**

Based on discipline

Nanotechnology and nanomedicine are highly interdisciplinary fields and this is clearly reflected in the definitions of nanomedicine.

Interdisciplinarity of the field

> Yes, the definitions of nanomedicine are diverse and that is probably due to the fact that the field in itself is highly interdisciplinary. We have chemistry, physics, and material sciences and then we have applications in biology, microbiology, biochemistry, medicine and pharmaceutical sciences. So, everybody of course has his or her own disciplinary background even though they work in nanomedicine and they

work with different definitions as far as understanding of the field is concerned. That is only natural. **R35**

In the context of this interdisciplinarity, a few respondents argued for defining the parent technology rather than the medical application.

I am not sure if nanomedicine exists as a separate thing. I believe there is nanotechnology that is used in nanomedicine. But nanomedicine should not be a discrete branch of therapeutic endeavor. So, the important thing is to try and define the technology rather than trying to partition a separate area in medicine because then technology can offer a huge range of different applications in different clinical circumstances. **R36**

A few respondents were critical of the focus on changed physical and/or chemical properties of matter at the nanoscale even though they understood its origin in the respective disciplines. They argued that biological properties are essential and more important than particle size to fully assess the breadth and scope of the field of nanomedicine.

For me biology has to be considered as well, especially the behavior and change of properties of these materials in interaction with biological systems. And I am fighting for increasing the upper limit from 100 to a few hundred nm; perhaps we could go up to 500nm because in biological systems, even particles larger than 100nm demonstrate the behavior of nano. Only if you double that, you go to one micron or 1000nm, they change. They don't penetrate the cell membrane like many nanoparticles do. So as far as the interaction of nano with biological system is concerned, the limit is higher, it is higher than 100nm. **R14**

Many of our respondents were vocal about the semantics of nanomedicine and how the terminology has evolved over last few decades.

Liposomes have been around since 1960s, but in last 20 years, they have been rebranded as nanomedicines or liposomal nanoparticles. I would say that for me it

should be below 150nm. What I do with *real (emphasis added)* nanotechnology is develop the materials whose properties are different because of nanoscale, for example, quantum dots. That is really nanotechnology in the sense that something happens to these materials because of their size. But, these things are much smaller; they are below 10nm. But, if you are in pharmacology, you can say that these nanoparticles follow the pharmacokinetics of a therapeutic compound and that is what I want to achieve. But, if you look at them from the perspective of physical chemistry, which I am also involved in, it becomes only interesting and truly nano at a scale about 10nm where the materials actually change their properties. So, it all depends on your perspective. **R28**

The view expressed above also shows the tension between the disciplines. The 'real' nanotechnology as perceived by professionals working in the field of physical chemistry as compared to the 'applied' nature in pharmaceutical sciences, which tends to be more open and inclusive of larger molecules up to a micron level, as long as these larger molecules can help achieve a desired therapeutic or pharmacodynamic effect.

Nano is an academic phenomenon

Respondents affiliated with large pharmaceutical companies often discussed the 'buzz' of nanomedicine as an academic phenomenon and pointed out that the label 'nano' has less importance in terms of drug development.

> Another problem is that this definition of nanomedicine is not really accepted by pharmaceutical industry. [The] "nano label" is dropped in industry when they begin drug development. Drugs are not developed as nano drugs; they are developed as drugs. **R11**

> There is a typical pharmaceutical approach to this definition. They consider all that is below micron that is below 1000nm as nano. So in that sense, their definition is not even compatible with the EU definition. **R15**

> The definition of nano as one to 100nm comes from National Nanotechnology Initiative. But it has no relevance to drugs or pharmaceutical products because drug companies don't care about size. They are more interested in creating safe, effective and superior drug formulations. So I think it is more accurate to use definition as one to 1000nm or below micron as far as drug development is concerned. **R31**

Based on audience

One of our respondents described how the audience he is talking to determines which definition he would use.

> From scientific (material science) point of view, we refer to nano if we have real change in properties and I use this definition when addressing scientific audience because they understand exactly what I am talking about. But, when I talk to the general public or medical doctors, I use the EU definition which states that half of the particles must be below 100nm because our more scientific definition is too complicated for them since we have a different value for each material at which the properties change. For iron oxide it is 20nm whereas for titanium di oxide it is about 10nm. To go further, while talking to pharmaceutical science people, I have to talk about definition, which is below a micron even though that definition is not compatible with EU definition. And then again, there is this political discussion about REACH [Registration, Evaluation, Authorization and Restriction of Chemicals] regulation. If you claim that the material you are working with is nano and has new properties, you are in danger that you have to show that this new material is safe and have to go through whole accreditation process under REACH. **R15**

Based on pathology and route of administration

An alternative definition of nanomedicines takes into account the pathology under consideration.

> The size definition is really arbitrary; nano aspect relates to the opportunities that the nature offers. If you think about an enhanced permeability and retention (EPR) effect, it won't work with your molecule, which is below 1000nm. You will need molecules that are in rage of 100 to 150nm or 50nm or even smaller. So I had rather use a more dynamic definition of nano related to what nature is enabling nano to do. If you have to treat a bacterial infection which is primarily located in macrophages in liver, then may be a formulation at 500nm is more appropriate in this situation because these particles containing drugs will get sequestered in the liver and you can also include higher amount of drug in these particles thus providing more effective treatment. **R24**

Another participant demonstrated how the route of drug administration would influence the definition.

> The particle size of below 100nm is crucial to achieve desired biological or therapeutic properties only when we inject the formulation systemically. But if you have an application where you can actually acquire particles locally, size is not as important as it is in case of intravenous application. In such a case, having larger particles is an advantage for they can accommodate more active drug ingredients. So for this specific application, I would say nanomedicine is to produce particles below 500nm. **R16**

Discussion

Nanomedicine is an interdisciplinary field and clinical translation involves multiple stakeholders. A crucial finding of our study is the extent to which stakeholders have described the tension between disciplines, target audiences and regulatory bodies when discussing the definition of nanotechnology and nanomedicine. This also highlights how difficult and challenging communication can be among stakeholders, especially if each has their own definition or understanding of nanotechnology or nanomedicine. We argue that clarity in the definition of nanomedicine and the consistent use of a single definition is critical to facilitate translational research in nanomedicine in ethical and transparent ways and to ensure a fair

distribution and utilization of available resources. As the field of nanomedicine acquires more knowledge and experience with different classes of nanoparticles, it is also critical that we start focusing on different classes of nanomedicines while discussing toxicity or drug regulation pathways, rather than assessing the whole range of nanomedicinal products with the same tests and against same standards. In this section, we discuss how various stakeholders have influenced the definition of nanomedicine, as well as the impact of multiple definitions on key stakeholders involved in the clinical translation in nanomedicine.

National and international scientific bodies and funding agencies

The establishment of the NNI in the US has clearly fueled research in nanotechnology and it's the medical applications. The NNI also created 'Centers of Excellence' in nanotechnology across the US and generated significant funding for research in nanotechnology (Roco 2011). Unlike biotechnology, which has mainly been supported by start-ups and private companies, nanotechnology has received significant public funding (Paull et al. 2003) as well as fostered a lager industry-academia collaboration (McComas 2012). Similar trends have been seen in Europe with funding from the European Science Foundation and the European Research Council as well as governmental funding schemes in Japan and South Korea (Roco 2005). As funding in the field has improved drastically, so has the number of grant applications. Scholars have also pointed out inadequacies in the current model of peer review based grant assessment and questioned whether commercialization of research is the best way to optimally utilize public funding in science and technology especially when some commercially non attractive yet needed research might never get supported by the industry (Spier and Bird 2003).

Many scientists working in various scientific disciplines have realized that the work that they have been doing for decades now could fall under the purview of nanotechnology based on nanoscale or if attributed to novel physical, chemical, or quantum properties of material (Drexler 2004). The work that was not originally labeled as nanotechnology or

nanomedicine has begun to be re-framed along these lines with the increased availability of funding. Increased funding in the field, coupled with increased media attention and broad definitions of nanotechnology and nanomedicine can create significant challenges for funding agencies to draw a cut-off point based on a definition alone when assessing these grant applications.

As shown in our results, many experts working in nanotechnology and nanomedicine have argued that a mere focus on size of particles is detrimental to a common definition because the change of properties in relation to size of the particle is a continuum rather than distinct size cut-off. They also claimed that in terms of an intervention sometimes size matters, sometimes changed properties are important and sometimes both size and change in properties are crucial to achieve a desired action. Clarity and consistency on a definition and special attention to size-based characteristics and changed material properties are crucial for funding agencies to distribute available funds across applications with the potential to improve healthcare and ensure transparency in the evaluation of submitted grant applications.

Patent authorities

Increased global funding for nanomedicine also has the underlying aim of improving and facilitating successful commercialization of technology to facilitate good returns on investments through public funding (Roco et al. 2011) This heightened focus on the innovation and commercialization of nanotechnology is also reflected in the increase in the number of broad patent applications related to investigational medical products, some aspects of the technology or the process of producing the product. Inconsistent definitions of nanotechnology and nanomedicine create confusion in the assessment and qualification of patent claims as well as drastically increased pending patent applications (Bawa 2007). Patent protection is particularly important for SMEs as it improves their chances of obtaining funding as well as enhancing the value of their product in the competitive world of drug discovery (Bawa et al. 2005). Patent related issues will become increasingly important as the

field anticipates the expiration of nanomedicine patents licensed in the 1990s and the future development of nanosimilars (Bremer-Hoffmann et al. 2015; Tinkle et al. 2014).

Regulatory authorities

Nanomedicines and their definition have significant implications for international drug regulatory authorities as well as industrial regulatory and environmental protection agencies. For drug regulatory authorities, it is crucial to account for the complexity of some of the investigational products based on nanotechnology. The drug-device distinction is not always clear, and with the advent of regenerative medicine, one could expect to see complex biological entities with cell-based components on a nano surface or nano scaffolds and other active molecular or chemical entities (Niemansburg et al. 2013). The characterization of nanoparticles has significantly improved over the last two decades, but the long-term toxicity of some nanomaterials still needs to be carefully assessed and will require stronger post-marketing surveillance. As described in the results section, various definitions of nanomedicine influence whether a molecule is approved in specific countries, depending on local drug regulatory authorities. Some authorities might be seen as less rigid and more inclusive in terms of the definition of nanomedicine as compared to the others. This could have an impact on the geographic location where trials will be conducted and new drugs will get licensed. Drug development and clinical research is an international enterprise and uniformity in a definition of nanomedicine across key drug regulatory authorities will facilitate translation of nanotechnology into clinical applications. The regulatory authorities need to carefully assess and monitor the use of nanoparticles in food additives, food packaging, and cosmetics as they fall into distinct categories of regulatory pathways and are often less strict than for the drug approval process.

Pharmaceutical industry and SMEs

As described in our results section, it appears that the label ‘nano’ is not significant for large pharmaceutical companies. However, it is crucial for SMEs that often work towards

producing ‘proof of concept’ in man (Eaton et al. 2015). SMEs depend on external funding to conduct early clinical translation studies, particularly for FIH trials. This funding comes from international grants or venture capitalists. Only on a successful ‘proof of concept’ in man can an SME out-license their product to the pharmaceutical industry or take the product further into phase I-II trials. The latter requires a large financial investment that SMEs can rarely manage to attract (Eaton 2012). Clarity and consistency in the definition of nanomedicine can improve the assessment for funding and allow SMEs to contribute to translational research.

Ethics committees

Clarity and uniformity in the definition of nanomedicine and the consistent use of nano terminology are critical for the ethical review of submitted clinical trial protocols. The role of EC is to ensure human subject safety while evaluating trial protocols involving patients or healthy volunteers. The EC needs to undertake a detailed risk assessment to balance the risks against the potential benefits before approving a clinical trial (Anderson and Kimmelman 2014). The EC also needs to carefully assess the informed consent forms and ensure that the risks and benefits of trial participation are clearly and accurately described in a language that is easy to understand (King 2012). If investigators do not describe the nanomedicinal product under investigation in all the necessary detail, it is likely to adversely affect the ethical review. Whether nanoparticles should be explicitly mentioned in the trial protocol, investigators brochure and informed consent form is a matter of debate and is beyond the scope of this paper. However, to ensure transparency and integrity in research, it can be argued that full disclosure of the nature of the molecule under investigation is needed for a rigorous ethical review (Dresser 2012) and to obtain a valid informed consent. Clarity and uniformity of the definition of nanomedicine would be important to facilitate transparency in clinical trials as well as in the ethical review of this research.

Patient population

Most nanomedicine has been developed for cancers where there is an unmet need for treatment. However, other chronic diseases are slowly being targeted by nanotechnology based improved therapeutics. In clinical translation and particularly in FIH trials, new interventions are often tested on patients who have no other treatment option (Hug and Hermerén 2011). Patients approached to participate in clinical research need to be provided with all the necessary information regarding the technology and the characteristics of the proposed treatment to make a truly informed choice. Many patients trust their physicians and hope to receive all the relevant information about the product under investigation from them (Anderson and Kimmelman 2014). But some may actually undertake internet research on their own. For patients to provide a meaningful informed consent, it is critical that they have all necessary information about the product they will be given and clarity on the nanotechnology-based formulation should be part of this information.

General public

Public acceptance of a technological intervention is essential for its implementation, improvement and access. The debate on genetically modified organisms in Europe, where the public was not clearly or adequately informed, showed the importance of honest and open communication. Literature on public engagement in nanotechnology has pointed out the need for such engagement (Cormick 2012; Cormick and Hunter 2014; Krabbenborg and Mulder 2015; Cacciatore 2014) and has also raised critical questions such as; what is the public? How does one engage those who are unengaged and what tools could be used to improve public engagement (Cormick 2009). Educating the public with the scientific evidence related to nanotechnology, and being transparent about the possible advantages and potential harms of a new technology is important (Priest 2009). Public opinion shapes the political and regulatory environment and influences the level of funding available for particular technology. Some of our respondents argued that nanotechnology is too complicated for the general public to

understand and that attempts to inform the public about the potential risks and benefits is likely to negatively polarize their opinion. However, this line of thinking is dangerous. Even if some patients and citizens do not understand the complexity of nanotechnology, assuming that no one needs to be informed compromises the public's right to information. With access to information and research databases, the public can obtain more information about a product or technology and might even feel deceived if certain information was underplayed by the scientists and experts. This action would erode public trust in science and prove detrimental to research and development (Master and Resnik 2013; Resnik 2011). It is important to find innovative ways to explain the complexity of nanomaterials and nanoparticles, and their potential use and risks to the public in scientifically accurate yet understandable ways. This could be achieved through various means such as school education and introducing children to basic concepts of nanotechnology, participatory interactions between the scientific experts and general public and by ensuring a balanced and scientifically accurate coverage of nanotechnology-related debate in media.

Limitations

To the best of our knowledge, no other empirical studies have looked at diversity in the definition of nanomedicine. Our purposive sampling technique allowed us to access a wide spectrum of viewpoints and strengthened our findings. However, there were 12 stakeholders who did not reply to our emails, phone calls, and letters. Whether the views of those 12 are drastically different from those of the 46 who were interviewed is unclear. The stakeholders we interviewed explained the refusal of the others in terms of extremely busy schedules and a preoccupation with higher priority tasks than contributing to this research project.

The aim of our exploratory qualitative research was to document the diversity in definitions of nanotechnology and nanomedicine and to examine how this affects translational research. Our research only focusses on stakeholders in Europe and North America and we are clearly missing the voices from China, Japan, Australia, India and other Asian countries

where research in nanotechnology and nanomedicine is ongoing. We do not claim that our findings can be generalized to all stakeholders of translational nanomedicine across the world. Further research with homogeneous populations such as SMEs, large pharma, scientists and academics using quantitative research methods is warranted.

The fact that one interviewer conducted all the interviews might raise a concern of systematic bias in the collected data; however we also believe that the consistency and standardization of the interview technique was an advantage. Open-ended interview questions allowed respondents to elaborate on their viewpoints and these expert stakeholders were unlikely to be influenced by the viewpoint of the interviewer. The difference in opinion of the interviewer and the interviewee in fact led to interesting debates that further teased out the nuances of the topic. Analysis of the interviews by generating codes and building themes was carried out by the research team to further minimize systematic bias that could have arisen if the data had been analyzed by only one researcher.

Conclusion

Nanomedicine is more than the application of nanotechnology in medicine and health care. It is a key enabling technology drawing on expertise and techniques from many scientific disciplines. It has attracted significant attention from funding agencies, policy makers and the general public, and has also been criticized as a buzzword or hype. For successful translation of basic science research in nanotechnology into clinical applications, transparency at each stage of technological development and trust among various stakeholders and general public are critical. This is where a clear, scientifically comprehensive and consistent definition of nanomedicine and further sub classification of nanoparticles used in medicines has a role to play. This definition and sub-classification will facilitate progress along the translational pathway without being too restrictive and improve communication across the stakeholders. This is not an easy balance. Convenient usage of one definition over others or dropping of word ‘nano’ when deemed unfavorable will prove dangerous in the long run as it will

adversely affect the public's trust and transparency in scientific research. An open and honest dialogue across the stakeholders, the general public and politicians is essential if we truly want to exploit the potential of this key enabling technology to improve human health and well-being.

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Chapter 4

Challenges of clinical translation in nanomedicine: A qualitative study

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Satalkar P, Elger B S, Hunziker P, and Shaw D. (2016) Challenges of clinical translation in nanomedicine. A qualitative study. Nanomedicine: Nanotechnology, Biology and Medicine. 12(4):893-900.

Abstract:

Clinical translation of breakthroughs in nanotechnology and nanomedicine is expected to significantly improve diagnostic tools and therapeutic modalities for various diseases. This will not only improve human health and well-being, but is also likely to reduce health care costs in the long run. However, clinical translation is a long, arduous, resource intensive process that requires priority setting, resource mobilization, successful national and international collaboration, and effective coordination between key stakeholders. The aim of this paper is to describe various challenges faced by the stakeholders involved in translational nanomedicine while planning and conducting first-in-human (FIH) clinical trials. We draw on insights obtained from 46 in-depth qualitative interviews with key stakeholders from Europe and North America.

Key words:

Translational research, nanomedicine, first-in-human (FIH) trials, challenges, qualitative research

Background

Translation of basic science research into clinical applications is known as translational research, and is crucial to improve human health and well-being.[1] Translational research facilitates the availability of improved diagnostic tests and treatment options, enabling early diagnosis, better treatment, and a consequent decrease in disease related morbidity and mortality. However, less than 10% of basic science research gets translated into clinical applications with a large proportion of promising experimental therapies not crossing the "valley of death".[2] This makes translational research a long, ineffective, and expensive enterprise which significantly increases health care costs.[3] In 2004, the US Food and Drug Administration (FDA) launched the Critical Path Initiative with the aim to improve the availability of new diagnostic and therapeutic modalities by systematically addressing some of the key obstacles in existing translational research processes.[4]

First-in-human (FIH) trials mark a critical juncture in translational research because it is at this point that experimental products get tested in human beings for the very first time. Though translational research in general involves significant levels of uncertainty, it peaks during FIH trials.[5] FIH trials get further complicated when the products under evaluation involve cutting edge medical technologies such as nanomedicine, synthetic biology, gene therapy, or cell therapy due to a lack of clarity on the mechanism of action and the exact target of the experimental product, and limited reliability and validity of preclinical animal models.[6]

The aim of this paper is to describe and discuss the challenges faced by stakeholders involved in translational research in nanotechnology. We chose medical applications of nanotechnology as a prototype and decided to focus on FIH trials. Nanotechnology has the potential to develop highly accurate and sensitive diagnostic tests,[7] targeted therapies,[8] and theranostic applications. [9] At the same time, there is a national and international focus on funding and research in nanomedicine with the hope that it will revolutionize our

understanding of diseases and advance our means to treat them.[10] Thus, researchers working in translational nanomedicine have to deal with high levels of uncertainty, the novelty of the technology, limited prior experience with nanoformulations and toxicity assessment, challenges in applying for and obtaining regulatory and ethics approval, increased media hype and heightened requests for scrutiny, while keeping in mind the unmet and pressing needs of patients living with chronic and terminal illnesses. A number of researchers and experts have reflected on challenges of translational research in nanomedicine [11-23] but our goal is to document these challenges by exploring the experiences and perspectives of key stakeholders who have either conducted a FIH trial or are planning one, and to propose possible solutions.

Methods

Qualitative research methods are employed to investigate topics where previous empirical research has been scarce.[24] We used semi-structured, in-depth interviews for this exploratory research project. We drew up a list of open ended questions to facilitate conversations with expert stakeholders involved in translational nanomedicine. This enabled respondents to freely narrate their experience and bring up topics, themes, and challenges that they deemed relevant. Three pilot interviews (with colleagues experienced in qualitative research and ethics of new technology) were carried out at the beginning of the project to validate and refine the interview guide, but were excluded from analysis. The research project, including the interview guide (attached in an annex), was approved by the ethics commission of Basel Land and Basel Stadt (EKBB) in January 2013.

We identified key stakeholders in translational nanomedicine through literature search and PS's participation in nanomedicine conferences such as CLINAM Basel, Swiss Nanoscience Convention and a meeting of the European Technology Platform (ETP) - Nanomedicine. These European conferences attract key stakeholders and researchers in nanomedicine from around the globe and reflect collaborative efforts made by the EU, the US

and other countries to accelerate translational research in nanomedicine. Rather than focusing on a homogeneous study population, we used purposive sampling to obtain maximum variation in views and experiences of respondents.[25] We contacted them either via email or in person during conferences and explained the aim of the research project, the process to be followed, and ways in which their confidentiality and anonymity would be ensured. We realized that building a relationship of trust with the respondents was crucial given that many of them were working on cutting edge research, were concerned about information they would share with us, and most importantly wanted to know how the data from the interviews would be used.

PS carried out 46 stakeholder interviews in English between October 2013 and November 2014. She obtained oral informed consent from each respondent before starting the interview. Whenever possible, she conducted interviews in person as this helped create a better rapport with respondents. She carried out 26 interviews either via telephone or Skype call when it was not possible to arrange timely travel to the location of the respondents. In line with qualitative research methods, we stopped recruitment when theoretical saturation was reached. Theoretical saturation is a point in time when the research team believes that in spite of interviewing more respondents, no new themes emerge for research questions being investigated.[26] All interviews were transcribed in full and we sent the transcript to each respondent to check the accuracy of technical details. Together with DS, PS analyzed all interviews by creating systematic codes and sub-codes, building them further into themes that were related to particular research question. Codes and themes were discussed within the larger research and author team to improve the rigor of the qualitative data analysis. Our goal is to discuss the range of views and experiences rather than the frequency of similar views. So instead of quantifying the results, we describe them in general terms (e.g. “a few,” “some,” “many,” “all”). For elaborating specific challenges in translational research, we chose the most comprehensive and detailed quotation from the respondents instead of providing four to

five quotations from different respondents who expressed similar views or experiences. We have described the methodology of our research projects in greater details elsewhere.[27]

Results

Our respondents were located in Switzerland, Germany, The Netherlands, Denmark, Norway, Austria, Hungary, Spain, Portugal, the United Kingdom, Israel, the United States and Canada. Their professional roles/affiliations and geographic distributions are shown in Figure 1 and Figure 2. Respondents were trained in medicine, molecular biology, biochemistry, material science, physics, toxicology, organic chemistry, pharmaceutical science, law, and ethics and had at least seven years of work experience in their respective field. Out of 21 investigators (affiliated with universities, SMEs or large pharmaceutical industries), 11 had conducted a FIH nanomedicine trial while the remaining 10 were in various stages of preclinical research. Nine out of 21 investigators were working on nanotechnology based cancer drugs, seven on immune mediated diseases and five were targeting infectious diseases. While the majority of our respondents were working with various types of liposomes (immunoliposomes, pH sensitive liposomes, thermosensitive liposomes), others had experience with gold and silver nanoparticles, super paramagnetic iron oxide particles, polymeric micelles, and SiRNA. The diversity in disciplinary background, geographic locations, and professional roles enabled us to gather views and experiences across a broad range of topics related to translational nanomedicine. To ensure anonymity of the respondents, we will use respondent numbers (e.g. R1, R2…) while describing results of this study. Nanomedicine is a small and close-knit community and detailed description of respondents in terms of their location or professional role can reveal their identity. Though this limits extent of our analysis, we believe that this is the most practical solution for our concerns regarding anonymity of respondents.

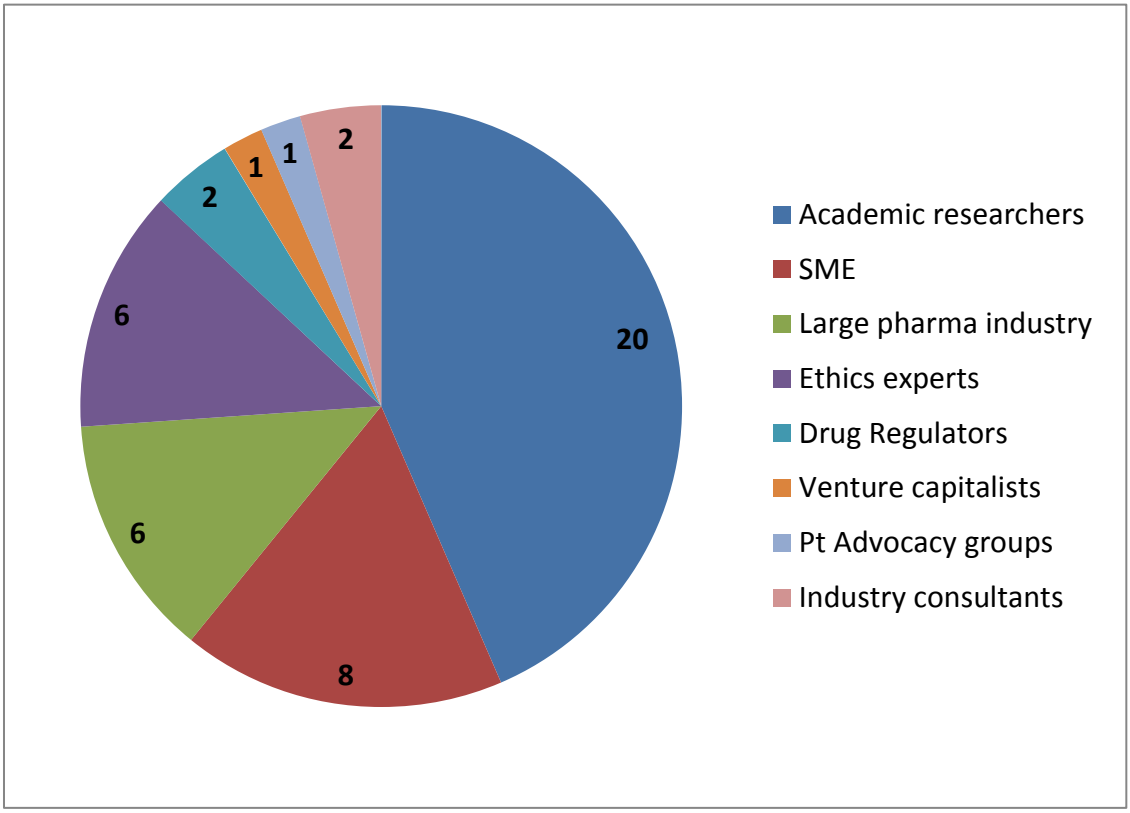

Figure1. Professional affiliations of respondents (N=46)

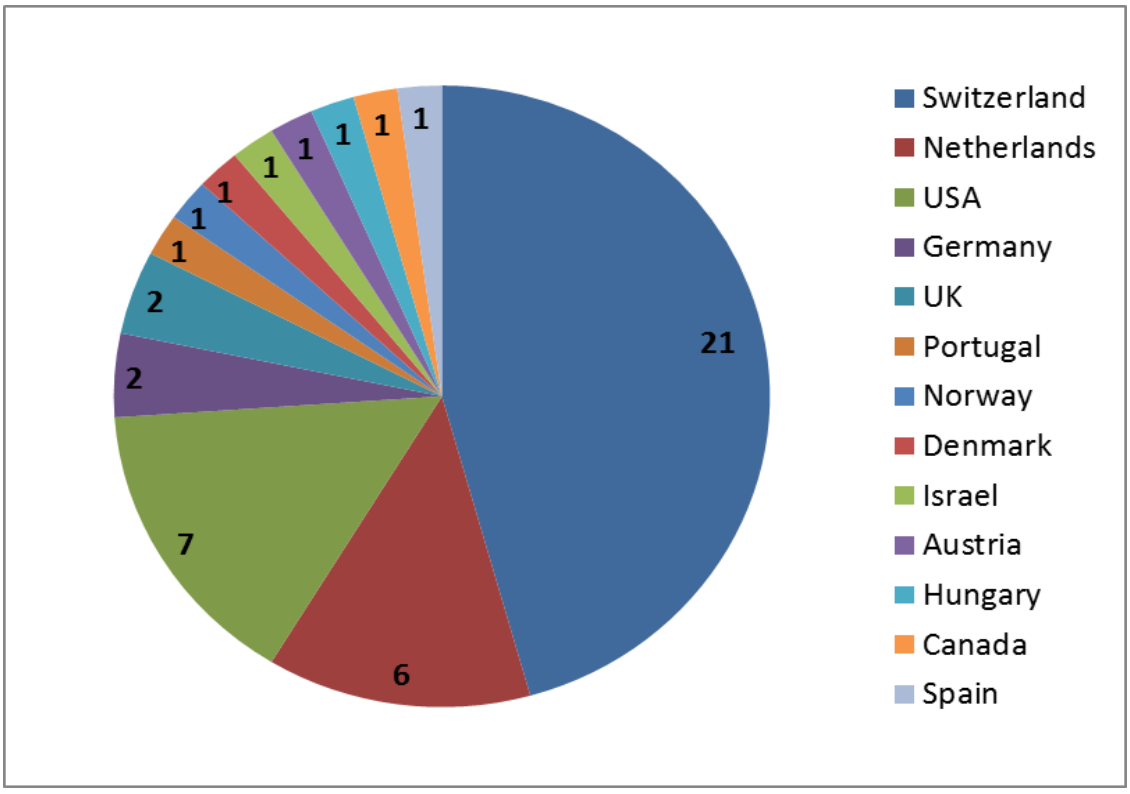

Figure2. Geographic distribution of respondents (N=46)

Financial challenges

Academic researchers and members of small and medium size enterprises (SMEs) experienced difficulty in securing the required finances. University researchers begin their basic science research with grants but developing it further into clinical trials requires additional funds. A researcher who conducted an FIH nanomedicine trial in a university hospital without an external sponsor told us that most of his team worked on this trial in their spare time. Scaling up good manufacturing practice (GMP) production at higher dose levels for this FIH trial required 9 to10 production cycles, each cycle requiring one complete week of work for five to six people. He stated that without any industry support, his team could not scale-up production and move further into phase II trials.

Scaling up GMP production of highly specialized nanomedicine products also requires substantial financial resources as described by a representative of a contract manufacturing organization (CMO).

> .. the supply chain can be a challenge because we are working in a niche, and can't get the raw materials from 10000 different suppliers. (…) we need to get all the documents needed for GMP production such as the Bovine Spongiform Encephalitis (BSE) certificate or certificate of origin for each raw material. (…) sometimes the client does not want to invest too much money at the beginning but wants from us the highest quality. And high quality needs full traceability right from the beginning. **R27**

Another university researcher further elaborated why one needs money to conduct a trial in a public institution.

> You need money to compensate volunteers, for the time they invest or the night they need to spend in the hospital (….) and you need money for insurances, because you need to cover any possible side-effects that you could cause to the volunteers. So, even if all the people involved are not requesting any payment, you need money. **R41**

Some university researchers secured more money by launching SMEs. SMEs play a crucial role in translational research but they continue to face funding challenges as well as pressure to complete trials quickly.

> And for a small company like ours, time is maybe the most important thing because …we have to show that we progress. We have limited amount of money from investors which does not last that long and before we can get more money from them we have to show that we have done something. And then we can't have two or three patients a year and then wait for five years to complete the study. That's impossible. Time is maybe the most important issue -to be able to get patients in as quickly as possible. **R34**

Several respondents mentioned that lower than expected patient recruitment prolonged trials and made them more expensive. Low recruitment was attributable to various reasons as described in the Table 1.

Table1. Slow/low patient recruitment

• (…) we agreed with the ethics committee to decrease the starting dose. But in the end that caused us a delay of a year because patients were hard to find. The dose level was so low that physicians were not keen on enrolling patients at low dose. **R2**
• One of the challenges, (…) is tumor heterogeneity. (…) we are taking advantage of the overexpression of a specific protein; we have to stratify the patients who actually overexpress on their tumors, that specific protein. And (…) it requires pretty strict and specific inclusion criteria or your particle won't work. **R16**
• The main challenge was that we did not get any patients. (...) the problem is our technology can only be used in a subset of patients. And you have to have quite strict inclusion/exclusion criteria. (...) It's logistically challenging (...). You have to have clinicians; a laser and everything which people are not used to using. This differs very much from hospital to hospital and the treatment such as ours involves different times and doctors. (...) So that's the challenge maybe especially for us because we have a technology that has to involve different kinds of medical professions and they do not always work well together. **R34**

While a large majority of nanomedicine has been developed for cancers, some respondents were working on other diseases such as arthritis, atherosclerosis, and diabetes. Unlike cancer trials, the primary and secondary endpoints for these trials are different and often require sophisticated imaging techniques within protocols, making the trials more expensive.

> In cardiovascular diseases, to look at these trials, they usually include 10000 patients with general cardiovascular drugs but with nanomedicine it is not possible, it is too expensive. We want to look at vessel wall, (…) rather than looking at the morbidity or mortality. That is a real challenge. These are very technical procedures so in addition to getting approval for a trial, you also have to integrate these imaging end points. And that makes it even more complex and even more expensive. **R28**

Interviewees mentioned that many national and international funding bodies continue to heavily invest in nanotechnology and nanomedicine through collaborative funding schemes and by establishing centers of excellence. Many respondents said they benefited from these opportunities but a few questioned the 'rationale of priority setting' at the policy level and the utility of spreading available money across many players in the field which they considered inefficient.

Researchers in large pharmaceutical industries also reported difficulties in attracting companies' attention towards their nanomedicine projects.

> Companies are not investing. If they have their own product already in the market they will not invest because they don't want to take risks. And new companies are very focused on their own products. The big pharma is buying products only if it is in advanced clinical status and very promising. **R24**

Another respondent explained how the pharmaceutical industry's traditional approaches to drug development do not encourage novel approaches in therapy and cure.

> In the past, the industry was prepared to produce chemicals; chemicals to kill some bacteria (…). Here in nanomedicine, we are confronted with something that is even more different. (…) We will need to rethink and produce. (…) Usually a pharmaceutical company would like to sell a product that is in a box and that has a very long shelf life. **R29**

Instead, stakeholders perceive large pharmaceutical companies to be interested in buying truly promising products developed by SMEs only after they have a strong 'proof of concept' in man. Which products developed by SMEs will gain the interest of large pharmaceutical companies and investors depends on their potential market share, competitive edge over existing products, and unmet treatment needs as shown in Table 2.

Table 2. Market interest

• I suppose the issues are rather market specific. … In some diseases, there are some really effective drugs under development, so it will be better to avoid those or your drug may not be competitive. Cost is very important. **R10**
• (…) USP means there must be a clear advantage against today's solutions. There are many possibilities why it is better. It could be cheaper, it could be quicker, it could be smaller, it could be more effective…depends! It must be in some way clearly better than what we have. **R17**
• …(one) problem is a lack of diversity. We have people developing very similar concepts for cancer. (…) The question of portfolio management as well is very difficult given the fact that many people abide the academic freedom. (….) relatively small number of drugs go to the market each year. If thousand people are doing drugs for cancer using the EPR effect, 999 of them won't be successful. Unless, they are having a really good idea, they should not be going in this area. **R10**
• People focus on clinical studies but it is not the goal and the end goal. For example if there are already three products on market, which work perfectly OK and you bring on the fourth, that product is not going to make any sales. So you have to know how the market is and your product has to be significantly better in some parameters than the products which are out there and also the cost has to be significantly reasonable. If the cost of your drug is astronomically high, then it won't sell. **R48**

Finally, patent protection for products under investigation was mentioned as another crucial point that determines investors' interest and researchers' chances of success in procuring the necessary funding to take the product further into clinical translation, as shown in Table 3.

Table 3. Patents and IPs

• IP is quite weak on this. This is not patented (….) because there are so many steps involved which are already patented, on liposomes, on antibodies, on construction. (…) there are more than 3000 conflicting patents so we were not able to have a strong patent and then you don't find funding from industry or interest of the investors. **R12**
• The technology is already very complicated because it involves also the heating equipment. So lot of companies will not be fond of that especially the pharma companies. And I believe that if it is not patented it will be really difficult to get the interest of pharma companies. **R8**
• I mean patents last only for twenty years. And if you don't have a patent then you use ten years of these years, probably even more to get a patent. Patents are often filed quite early in the preclinical studies and then you use some years for developing pre-clinically and then you use a lot of years for getting it approved clinically. And there are not that many years left. **R34**

Ethical challenges

Risk/benefit evaluation serves as the foundation of ethical review. Most FIH trials in nanomedicine are conducted in patients who have exhausted all other treatment options. Due to the design of these trials, patients are unlikely to receive therapeutic benefits but the data gathered is valuable in terms of knowledge gained. In early clinical trials of cutting edge medical technology such as nanomedicine, assessing risks, benefits/harms, and knowledge gain poses significant challenges.

> The biggest single challenge is the problem of risk. Now in life and in all sectors of human activity, (…) we encounter risk that is in a sense calculable. And when you are working within a realm that is highly novel like gene therapy or novel stem cells approaches or nanomedicine, you are dealing with circumstances where it is very difficult to calculate the risk. And it is also unclear what the appropriate evidence to be used is, on which one can base their risk decisions. In addition it's also difficult to calculate utility, to calculate value. And it's hard to know which kind of evidence to draw on to calculate the value. So it's a realm that is ripe with arbitrary decision-making (…) And because there is no clear well-developed framework or structure for making the risk benefit decisions, one of the biggest challenges is trying to control or limit extent to which decision-making is utterly arbitrary. **R42**

Our respondents were divided on role of ethics committees in translational nanomedicine. Some had smooth interactions with ethics committees while others perceived them to be risk averse and paternalistic, thus slowing down translational research. Some of our respondents believed that ethics committees do not intentionally block translational research but their role requires them to be "cautious" and to strictly follow available guidelines to ensure human subject safety. Others criticized the tendency of ethics committees towards what they considered to be "exaggerated caution", especially when there were no treatment options for the suffering patient population; argued for meaningful patient involvement in the ethical evaluation of trials; and highlighted the need for a broad stakeholder discussion.

> Long term implications of new medical technologies are often poorly understood. This in turn, possibly creates a climate erring on the side of caution. (…) there is a perception that maybe the ethical choice is to do nothing rather than to allow the proposed trial to go ahead. Whereas from a patient perspective, those living with or caring for someone with a life limiting disease (…) would like to have the opportunity to make that choice for themselves. The regulators and ethics committees tend to be

> cautious as they have a role in protecting patient safety. But the balance between benefit and risk needs to swing. (…) If you are dealing with people with a life limiting disease, then they may have a different view on the amount of risk that they are willing to take in return for the possibility of a benefit which they would value. So it is important to look at the issues from the perspective of patients as well.**R36**

Physicians interviewed in this study agreed that patients had an important role to play in translational research. But they also described their struggle to explain to patients the trial design, risks and the unlikely possibility of benefit from the FIH trial. One of their major challenges was to provide technically correct information without completely destroying patients' hope. They often wondered if patients really fully understood the procedure and provided truly informed consent.

> What I personally find a bit difficult is that you have to explain the trial to the patients. (…) patients may be hopeful that the trial is doing something good, (… but) as an investigator you (…) know chance of 10% or 20% of any benefit. (…) And you have to tell them, (…) you won't have any benefit, but you will have toxicity. I think it's quite a difficult discussion, because you don't want to take away any hope from the patients, but at the same time you have to tell them that there is a fair chance it's not going to help. **R3**

Regulatory challenges

All respondents acknowledged the critical role played by drug regulatory authorities in early clinical translation. Most of them had established contact with the authorities early on in trial planning and found it extremely useful to keep regulators "on board." They felt that the scientific advice and pre Investigational New Drug (IND) consultations with the authorities were extremely valuable for them to prepare for their trial. But they also criticized regional and national differences within and between regulatory authorities and their individual requirements, which were often quite distinct. This posed a significant challenge for researchers running multicentric international trials. Depending on local regulatory requirements, they sometimes needed to amend their protocols but then ended up with different protocols at different sites.

Respondents planning to conduct trials in developing countries reported having received less support and guidance from regulatory authorities, which they attributed to the fact that these authorities do not have much experience with nanoparticles and formulations and take a rather precautionary stand. Researchers using nanotechnology to work on therapies for neglected diseases particularly saw this as a significant challenge.

Respondents mentioned nanocharacterization and toxicological tests as another major challenge. European researchers mentioned this problem more often than their American colleagues. European scientists working on nanoparticles reported having been required to bring the tests and assays to prove that the particles under investigation are safe, but also acknowledged the EU's efforts to strengthen nanocharacterization capacity in Europe in collaboration with Nanotechnology Characterization Laboratory (NCL) of the United States.

> (…) besides GMP-production, we have to show that the typical tox-tests which are developed for chemicals and molecules, are also useful for nanoparticles and if not we have to propose to drug regulatory authorities an alternative method to check the toxicity of the particles. This is the big, big hurdle. For example, a lot of tox-tests are based on colorimetric methods and iron oxide is brown. So a lot of colorimetric methods simply do not work for our particle. **R15**

While discussing FIH nanomedicine trials conducted in Europe in early 2000, one of our respondents highlighted the distinct regulatory pathways for drugs and devices. These regulations change over the course of time and can significantly affect the progress of certain products along the translation path.

> (…) they are working now 20 years in this field. And at *that time* (emphasis in original) they were able to show that their particles are a device because they inject it directly into the tumor and particles stay in the tumor. With a device, much easier! Swiss and European authorities now handle nanoparticles even for diagnostic application as a medicament. So we have to do more preclinical work with the nanoparticles even if it's a device as compared to at the *earlier time* (emphasis in original). **R11**

Another respondent raised concerns about regulatory pathways to govern follow-on versions of licensed nanomedicines and nanosimilars.

> …one of issues with either the biologics, the non-biologics and clearly as well with the nanomedicine is that the approach of the regulatory agencies is similarity approach than the sameness approach. Meaning that for follow-on versions, we will never have the same but some similar products, which could lead to question- what is similar enough to get a kind of therapeutic alternatives or therapeutic equivalence allowing even to switch between the test and reference product or even interchange them? (…)This is big challenge and contrasts the generic paradigm. (…) one has to go to clinical head to head analysis for comparability evaluation which could finally make follow-on products not a cheaper alternative. **R32**

Discussion

Slow and scarce translational research is a global concern due to its adverse impact on the availability of affordable and effective treatment options. The financial, ethical, and regulatory challenges presented in this paper have been discussed extensively in the literature on translation of other cutting edge biotechnologies such as gene transfer,[5] cell therapy,[28-31] and regenerative medicine,[32-33] but our study is the first to actually investigate the experience of those involved in translational nanomedicine. This allowed us to understand the tensions underlying these challenges and to seek solutions which will be relevant for medical applications of any cutting edge biotechnology.

In spite of increased national and international collaborative funding schemes, all respondents of this study, irrespective of their affiliation with the universities, SMEs or large pharmaceutical companies, perceived it challenging to procure the necessary funds to initiate a FIH trial. Though many academic researchers are successful in basic science research, they often lack the capacity, experience and insight necessary to launch FIH trials.[34] Personnel experienced in clinical research are often in short supply in university hospitals due to existing high workload in patient care and priority on treatment over research. Furthermore, the turnover of hospital staff can adversely affect quality standards in clinical trials. These challenges significantly affect translational research in university settings in spite of availability of interdisciplinary expertise and access to patients. In this context, it is important to find ways to motivate academic researchers to continue working in translational research and create an environment in universities which is more conducive to conducting early

clinical trials. Another approach could be to strengthen the capacity of academic medical centers to undertake translational research through dedicated funding schemes and infrastructure development. Hospital pharmacies need to be strengthened to produce needed quantities of doses under GMP conditions. A certain percentage of hospital staff could be designated for clinical research. This would require innovative funding avenues that go beyond National Science Foundation grants which have reduced significantly in both size and number in recent years due to changes in policies for public funding in education and research.[35-37] Philanthropic organizations could play a financial role in strengthening the translational research capacity of university hospitals and academic medical centers.

Many university researchers have tried to overcome financial hurdles by establishing SMEs. In spite of having an increased chance of being funded by venture capitalists, SMEs struggle to procure enough funding to obtain a "proof of concept" in man. As our results show, the interest of venture capitalists in products heavily depends on their potential market share and returns on financial investment. This means that only products that can provide a good return on an investment are likely to get funded in the first place. This implies that treatment options for certain diseases or conditions that are financially lucrative are more likely to progress along the translational pathway, while treatment options for neglected and rare diseases will continue to remain on the periphery. Some universities have tried to overcome financial challenges by commercializing technology developed in-house through 'tech transfer' departments, but this leads to other intellectual and financial conflicts of interests[38-39] when investigators and inventors become too closely involved in translation research as was the case in 1999 with the gene transfer trial for ornithine transcarbamylase deficiency.[5, 40]

Large pharmaceutical companies are probably best placed to take on a major role in early translational research. However, as respondents of this study reported, the pharmaceutical industry seems to be rather reluctant to venture into early clinical translation

of nanomedicine. Given the high uncertainty involved in novel technologies and financial stakes, they are willing to buy only promising products for which a "proof of concept" in man has already been obtained. But it is extremely difficult for the academic researchers or SMEs to produce a "proof of concept in man" without substantial funding and technical support, thus creating a catch 22 situation. It might be worthwhile to think of ways to motivate large pharmaceutical companies to take a more facilitatory role in translational nanomedicine research.

Drug regulatory authorities undoubtedly play a major role in facilitating translational research in nanomedicine. As scientific knowledge evolves at a rapid pace they need to keep themselves up-to-date on all the technological developments in the field as well as advances in regulatory science. [41] The US FDA and European Medicines Agency (EMA) differ in their definitions of nanomedicine and their requirements for the evaluation of new investigational drugs. If every national or regional drug regulatory authority has its own understanding of what constitutes a nanomedicine and what regulatory pathway such a product should follow, it becomes challenging for researchers to coordinate FIH trials in multiple jurisdictions. Some regulatory authorities might be seen as less restrictive and hence such countries can become "favorite" destinations for conducting FIH trials. It will also become more challenging to distinguish between drugs and devices as multiple technologies converge to produce medical applications; this has already occurred in regenerative medicine where nanostructures or scaffolds are used in combination with biological cells. Another challenge that lies ahead for drug regulatory authorities is the assessment of nanosimilars in comparison with the original drug produced with nanotechnology.[42] Drug regulatory authorities will need to prolong and strengthen post marketing surveillance of nanomedicinal products to monitor long term toxicity profile in patients, especially for chronic diseases where patients will consume the drugs for a prolonged period. Finally, it is critical to build regulatory infrastructure in

developing countries so that they can locally assess and evaluate FIH trials for disease indications that are prevalent in their context.

It is essential to simultaneously establish strong ethical oversight to evaluate clinical research with investigational nanomedicinal products. In some countries, ethics committees only evaluate ethical aspects of FIH trails such as risk/benefit evaluation and readability of informed consent forms while in other countries, they are also expected to assess the scientific evidence upon which risk assessment is based. In both cases, it is critical that at least some members of the ethics committee are capable of critically examining the science and accuracy of preclinical evidence, and of undertaking comprehensive risk assessment in a context where uncertainty and ignorance regarding potential harms is significant.[43] In countries where few FIH trials in nanomedicines have already taken place, it might be worthwhile to develop national ethics oversight bodies that could assess proposals and systematically document the procedure of risk assessment as well as experience gained from these trials. That national experience and expertise could then percolate down to regional and institutional ethics committees through systematic training and knowledge transfer so that eventually such FIH trials can be evaluated in decentralized ethics committees. Data safety monitoring boards and robust reporting systems for adverse events need to be strengthened to ensure human subject safety.

Effective collaboration between pharmaceutical industry, SMEs, academics, drug regulatory authorities, ethics review committees, patient organizations, and policy makers is essential for strengthening translational research in nanomedicine. Professional organizations, such as CLINAM, Basel and ETP-Nanomedicine, have played a significant role in facilitating translational nanomedicine in Europe by generating multi-stakeholder debate, fostering effective collaborations within EU and globally and actively engaging with policy makers with the aim to find solutions and speed up clinical translation.

Limitations

To the best of our knowledge, this is the first exploratory qualitative study investigating challenges in translational nanomedicine. The results of this research provide interesting insights into stakeholder experience, but generalizability is limited due to qualitative methodology and purposive sampling technique. Those who agreed to be interviewed had a certain interest in the topic and hence their views might be different than those who refused participation. Our strategic focus on Europe and North America means that we missed direct views from other countries such as China, India, Australia, and Japan. However in light of globalization we would have expected at least some remarks of our interviewees to point out huge differences in Asia and Oceania, and have therefore reasons to believe that general challenges related to translational nanomedicine in those countries are largely similar.

Our study has identified key challenges in conducting translational nanomedicine research. We have suggested some ways to overcome these challenges. Further quantitative research with a global study population is warranted to systematically document differences attributable to national regulatory environments, funding opportunities, and experience of local ethics oversight.

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Chapter 5

Naming it ‘nano’: Stakeholders’ views on use of ‘nano’ terminology in informed consent forms of first-in-human trials in nanomedicine

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Abstract

Background: Obtaining valid informed consent can be particularly challenging in first-in-human (FIH) trials of medical applications of nanotechnology due to the complexity of interventions, the hype and hope concerning potential benefits, and fear of harms attributed to 'nano' particles.

Aim: The aim of this exploratory qualitative research paper is to describe and analyze the opinions of expert stakeholders involved in translational nanomedicine regarding explicit use of 'nano' terminology in informed consent documents.

Methods: We draw on content analysis of 46 in-depth qualitative interviews with key stakeholders in translational nanomedicine based in Europe and North America.

Results: We received a spectrum of responses ranging from reluctance, across more ambivalent reactions, to absolute insistence on explicit mention of 'nano' in informed consent forms. A variety of reasons for these beliefs were offered by participants.

Conclusion: Our analysis concludes that consistent, clear and honest communication regarding the 'nano' dimension of investigational product is essential in patient information sheets and consent forms for FIH trials. Complete exclusion or underplaying 'nano' for any reason is dangerous. It would not only threaten the validity of informed consent but also adversely affect public trust in science, technology and the clinical research enterprise.

Key words

Informed consent (IC), participant information sheets, First-in-human (FIH) trials, nanomedicine, nanotechnology, qualitative research

INTRODUCTION

Many international [1-3] and national [4-5] ethical guidelines mandate that researchers obtain valid informed consent from research participants. For informed consent to be valid, the individual must be competent, comprehend the information provided and agree to participate voluntarily. The investigators are required to provide complete and correct information about the investigational product, anticipated risks and benefits and disclose any conflicts of interest, in language that is understandable by lay people. It is not always easy to fulfil all the criteria mentioned above and scholars have highlighted various challenges involved in obtaining valid informed consent [6-10].

It is particularly challenging to obtain valid informed consent in first-in-human (FIH) clinical trials. These trials pose the highest level of uncertainty in terms of risk, and the trial participants are unlikely to receive any clinically relevant therapeutic benefit as most of them receive sub therapeutic dose in this dose finding study [11]. FIH trials are often conducted on healthy volunteers or terminally ill patients who do not have any treatment options. Scholars have analyzed extensively whether these groups of trial participants are capable of giving a truly informed consent and ways to minimize the threats to informed consent due to the financial motivation of healthy volunteers and the inability of terminally ill patients to distinguish between research and treatment, when their misplaced and overtly exaggerated hope can lead to the therapeutic misconception [12-15].

In this research, we investigated the ethical challenges experienced and perceived by stakeholders involved in FIH trials of nanomedicine. Nanomedicine, which is usually defined as applications of nanotechnology in medicine, is considered to be a key enabling technology with the potential to significantly improve sensitivity of diagnostic tests, allowing early disease detection and development of highly effective and targeted drugs providing better treatment options [16]. The last two decades have witnessed tremendous hope and hype

around the potential of nanotechnology and nanomedicine [17]. There are also critical voices concerned about nanotoxicity and the long term effects of nanoparticle exposure on humans and the environment [18-21]. ‘Nano’ has become a buzz word and has been associated with two extreme ‘images’- one as a magic bullet that can solve a number of problems faced by humanity and the other, darker ‘grey goo’ scenario with uncontrolled replication of nanoparticulate material destroying humanity. We wanted to explore how the word ‘nano’ plays a role in FIH trial related documents such as grant applications, research protocols, investigator brochures, informed consent forms and scientific publications.

The aim of this paper is to analyze the reasons provided by respondents in favor of and against explicitly mentioning the fact that FIH trial involves ‘nano’ (nanocarrier, nanoparticle, nanoformulation or nanoproduct) in informed consent (IC) forms, and to discuss its implications on validity of informed consent as well as trust in clinical research.

METHODOLOGY

Our exploratory qualitative research aimed to investigate the ethical challenges faced by stakeholders involved in FIH trials in nanomedicine. In-depth interviews allowed us to gain insight into the experiences, values and arguments of stakeholders, rather than quantitatively assessing their views.

Study population

We identified stakeholders in translational nanomedicine in Europe and North America through a literature review, participation in key nanomedicine conferences, university collaborators and professional networks. We interviewed scientists working in universities, large pharmaceutical companies, small and medium size enterprises (SMEs), ethics experts from national ethics advisory committees and institutional/hospital ethics committees,

representatives of drug regulatory authorities, clinical research organizations (CROs), contract manufacturing organizations (CMOs), patient advocacy groups, and venture capitalists.

Study instrument

A literature review on ethics of translational nanomedicine helped us to develop a list of open ended questions that we used to facilitate the interviews. It steered the discussion and also provided the respondents an opportunity to describe issues that they considered relevant to the topic under discussion. The interview guide was pilot tested and validated with three colleagues (experienced in qualitative research and the ethics of medical technology). The pilot interviews were excluded from the final data set.

Interview and transcription

Between October 2013 and November 2014, PS[1] conducted 46 stakeholder interviews in English either in person or through a phone or Skype call using a maximum variation sampling and a snowball technique [22]. She obtained an oral informed consent and permission to record the interviews from each respondent before the interview. We anonymized the data to ensure confidentiality of participants' identities and views. The interviews lasted on an average for 50 minutes depending on the time availability of the respondent, their interest in the topic and willingness to share their experience. We continued to recruit respondents for interviews till theoretical saturation was reached. Theoretical saturation is a point in qualitative research when the researchers feel that no new themes relevant to topic under discussion emerge in spite of continuing interviews with more respondents [23]. PS together with research assistants transcribed all interviews in full and sent the interview transcript to each respondent to check the accuracy of technical content.

[1] PS is a physician and medical anthropologist. She is trained and experienced in qualitative research methods and is a doctoral researcher on this research project.

Data analysis

PS carried out research question guided deductive coding of qualitative data using software MAXQDA. DS undertook a similar coding exercise manually. The research team compared and discussed the codes and the themes generated by these two approaches till a consensus was reached. This was one of the ways to improve the rigor of content analysis by minimizing misinterpretation of data and influence of researcher's personal biases. In line with reporting format of qualitative research, we will present our results using select quotations from the respondents to highlight various perspectives of the stakeholders. Since it is an exploratory research study, our aim is to show the spectrum of perspectives rather than quantifying their frequency. We use a limited number of quotations from our data set that are most comprehensive and provide interesting insights and exclude similar thoughts expressed by other respondents to avoid repetition. To protect the anonymity of stakeholders from close knit translational nanomedicine community in Europe and North America, we present their perspectives with respondent numbers such as R1, R2 rather than describing their profile in details such as physician from the Austria working on thermosensitive liposomes or ethics expert from Swiss National Ethics Commission. Though, it limits the extent of our data analysis, we believe this is the best way to ensure confidentiality and anonymity of our respondents.

Ethical approval for the study

The research project and the interview guide were approved by the local ethics committee in January 2013.

RESULTS

Our aim was to assess the views of respondents regarding explicit mention of nanoparticles or nanoformulation (referred to henceforth as 'nano') in participant information sheets and

informed consent forms of FIH trials. We received a spectrum of responses ranging from ‘there is no need to use word nano’- (reluctance), across more ambivalent reactions, to ‘it is absolutely necessary to be honest and explicitly mention the word nano’-(insistence). In this section, we present some of the responses that represent different contextual arguments and also highlight challenges in ‘informing’ a trial participant and being an ‘honest and transparent scientist’.

Reluctance

Reluctance to explicitly mention ‘nano’ was attributed to two main reasons. First, the complexity of the technology makes it difficult to adequately inform trial participants without overwhelming them with information. The second reason was the failure of the general public to distinguish between highly regulated nanomedical and nanopharmaceutical products and the unregulated (or minimally regulated) use of nanotechnology and exposure to nanoparticles in everyday life (in cosmetics, toothpastes, food packaging, lightweight bike frames, detergents, wrinkle free clothing, stink free socks, water resistant paints, stain free fabrics, traffic pollution, dust generated while printing, waterproofing shoe sprays) which often leads to misplaced fear about nanotechnology and nanoparticles.

> I don’t think the patient understands what nanoparticles are. It is hard for us to understand what that means. I would not be able to explain to a patient what a nanoparticle is except that it has a size of 55nm and it is between 1 and 100 nm and that is why we call it nanomedicine. **R6**

> So if there is nothing useful to gain by putting ‘nano’ in informed consent form, I will *not* (emphasis added) because people don’t understand anyways. There is a big difference between the nano pharmaceuticals sector and nanomaterial side and we have to make a clear boundary between the two because one is unregulated sector and

pharmaceutical is highly regulated sector. So the danger is that people confuse between the two. **R10**

Ambivalence

The responses taking the middle ground regarding the use of 'nano' reveal the ambivalence and conflict felt by stakeholders. Most of our respondents fell into this category, for various reasons described below.

Attributes of nanotechnology and nanoparticles in investigational product

Respondents referred to the technological aspects of nanoparticles, such as size, changed physical, chemical and electric properties, their impact on targeted drug delivery and potential adverse effects. Respondents said that they were more likely to explicitly refer to 'nano' if the desired characteristic of investigational drugs could not be achieved without nanotechnology.

> I would say that 50% of myself goes to each side. I agree that you could just describe the formulation and say it is composed of polymer which contains a drug and so on. So you don't tell all the truth. But then if you are really exploiting the beneficial features of the nano, I think at that point you need to specify that to the volunteers, because otherwise it's not fair. You need to be clear enough for them to understand what you are doing. But again maybe you don't need to explain too much. **R41**

> I mean if the nano doesn't mean that you are going to put the volunteers or the patients at risk then you could avoid mentioning that. But then if you are in a situation where the nano could be really the key in adverse effects, so yes. I would probably tend to mention this in a very smooth way not to make people concerned or be alarmed. **R7**

> We are producing nano and what happens to it in the body? Is it still nano there? Or does it agglomerate? And from that point of view, I would probably give it an artificial

name like we say aspirin. We do not say Salicylic acid. Because it does not matter what it is exactly in its form or in its chemistry. If for the patient, it is recognizable with a name, and he or she knows “this is the good medication that I need or this is the compound that is active...” Then that’s fine. **R35**

Context of the trial participants/patients

Other factors that influenced whether or not to mention ‘nano’ in trial documents were characteristics of trial participants (patients vs healthy volunteers) and the type of disease. Often our respondents advocated for a case by case approach to assess the needs of each group of participants.

Right... if it’s a nanotreatment, it depends on the situation of that person. He or she will consider it either as something: “yes, let’s try it” or “oh my god!” But on the other hand, I mean any compound that is currently used for chemotherapy for instance, they are toxic, they are not really good. And if you look at the side effects, it’s enormous and still these compounds are being accepted as treatment. They cure the cancer but they also do a lot of other damage in the body. And yet it is accepted. So I guess, if it is then called nano or something else, it would not matter in this kind of first trials. **R17**

I guess that is partially right, but on the other hand nanomedicine opens new perspectives and innovation and could be in a way a personalized medicine’s approach. In addition patients affected by severe chronic diseases often know a lot about their illness and ongoing research. So informed consent might be very important to explain such trials and patients understand the trial quite well. In addition if the patient gets some knowledge about the potential drug he will be exposed, he will probably inform himself e.g. on the internet but a large part of this information might

not be peer-reviewed and it makes it difficult to get right information and conclusions drawn by the patient might not be correct.... And to do that, I guess you have to inform participants respecting their knowledge and understanding but probably as well the urgency of this kind of treatment for these patients... So again probably a little more individualized approach is needed. **R32**

Hope, hype and buzz of 'nano'

Some of our respondents highlighted the semantics around nano and nanomedicine, arguing that liposomal drugs were licensed and used before the terms nanotechnology and nanomedicine became mainstream. It was seen appropriate to refer to nanotechnology and nanomedicine with a scientific audience but not with patients or trial participants.

Ah…I don't know...But maybe no. I don't think I would call it a nano product. Why should you? (Giggles)...I mean....Nanotechnology.. Maybe it's important to use the word in scientific settings, but for the patients I don't think it should matter whether it's a nano or whatever it is as long as you have the necessary tox studies and the necessary approvals and so on. But maybe, maybe one should do that because people could come afterwards and say to you: "Why didn't you tell me this was a nanotechnology product?" But...I don't know. At the same time there are of course a lot of nanotechnology products further down the translational pathway.. in market: liposomes, that kind of things which are nanotechnology products but which were there even before they invented the nanotechnology term in a way. **R34**

That's a very tricky question. This has to do with the word nano. And the way it is being abused all the time and scaring people all the time. And...So I think as a scientist, you can just describe the particle. However, as a person, I would not feel correct if I would do so. So..if I had designed such particle, I would just choose for the

word nanomedicine, but I would describe it such that I would explain it very clear in a layman language to the patient that, it has been investigated very properly and that we have a good hope that it would work, if that's the case of course. Because I don't like to lie to patients at all. So I would use the word nanomedicine and I would take the risk in having fewer patients or make more effort in getting patients to enroll. **R26**

Insistence

Those who strongly believed that they will explicitly mention the word 'nano' in informed consent forms attributed it to honesty and transparency on the part of scientists and its crucial link with building public trust in science, technology and clinical research enterprise.

Absolutely, absolutely! I think the worst we can do is to be not transparent. We need to be transparent as scientists. I feel if you ask patients to volunteer, they have an interest in knowing what is being done. And some patients might also be very proud; oh we are testing something very new. So why not provide that information to the patients. If it is a nano drug then it's a nano drug and we should be transparent. And I think any efforts to be non-transparent in any community on a long-term always harm the community. **R40**

No, I think this is not fair. I don't know if our ethics committee would allow that. I would stand up there and say: "no". If you have a patient or a healthy volunteer offering his or her help to you so you can perform your experiments or your trial, you have to inform people. You can convince them; you can tell them and just provide them with the data which are available. But I think you should not hide anything. Could you imagine a year later, or half a year later, this is found out? No, I think there you have to be transparent. **R20**

> Yes, I would definitely use that word but thereby also explain it in very general knowledge language, not very scientific language … nano is only the reference to size and has nothing to do with very dangerous materials that can induce cancers… and based on the data we have obtained in the animals, we have seen improved added value. I think one should be honest about it and not put it under the table. **R21**

DISCUSSION

To the best of our knowledge this is the first empirical qualitative enquiry to investigate stakeholder's opinions on explicit mention of word 'nano' in informed consent (IC) forms and the arguments underlying them. It was also an opportunity for respondents to reflect on their beliefs and share their concerns about being completely honest, as explicitly mentioning 'nano' in IC forms could mean challenges in patient recruitment due to fear. At first glance, the reluctance regarding mentioning 'nano' demonstrated by a few researchers and the ambivalent position taken by a majority of respondents could be considered disappointing given that we would expect researchers to have a better understanding of the requirements for informed consent [13,24], but the reasons provided by them point to larger conflicts that need systematic attention, including the hype and hope generated by nanotechnology, funding politics, public engagement in science, balanced science communication, involvement of multidisciplinary teams in translational research and training of drug regulatory and ethical oversight authorities [25].

It was not surprising that those who were reluctant to mention 'nano' were concerned about the complexity of technology and fear about nanotechnology in society, whereas those who argued for explicitly mentioning 'nano' in trial related documents often referred to transparency, honesty and research integrity. When asked about ways to address public fear so that scientists can be honest and transparent in trial related documents, all of them advocated better public engagement, responsible and balanced media coverage and highlighted the role

of scientists in science communication. They felt that underplaying the word ‘nano’ for short term goals such as faster patient recruitment, would not only compromise their research integrity but also adversely affect public trust in nanotechnology and clinical research in the long run. They saw a significant role for themselves in public engagement and science communication and were seriously concerned about the unbalanced media attention received by any cutting-edge medical technology or biotechnology [26]. Small breakthroughs and success in preclinical research published in prominent scientific journals can be sensationalized in mass media as if similar success in humans is just around the corner, thus wrongly raising the expectations of patients and falsely fuelling their hope. It was also a shared experience of these stakeholders that negative results (especially when a particular nanoparticle is proven to be safe in humans) are difficult to publish, unlike the research that proves toxic effects of particle under investigation, further polarizing the media and common man’s image that most ‘nano’ particles are dangerous and toxic. Their recommendations to minimize public fear included ‘case by case’ assessment of each nanoproduct and development of robust systems to monitor and evaluate long term effects of nanoparticles in human beings and the environment.

The other main interesting finding of this study is the ‘ambivalence’ felt by the stakeholders regarding explicit mention of the word ‘nano’ in trial related documents. Their arguments were more diverse, covering semantics of ‘nano’ in nanotechnology and nanomedicine, the contribution of nanotechnology towards beneficial and toxic effects of investigational products, and whether the product was used on healthy volunteers or terminally ill patients. Their opinions were rather fluid and were likely to swing more towards ‘reluctance’ than ‘insistence’ as far as IC forms were concerned, implying that as long as the participants understand the stakes, it was secondary whether the word ‘nano’ was mentioned explicitly. This could also mean that the trial participants would be less likely to get distracted

by the technical jargon of ‘nano’ and images associated with it and understand the trial information better. But it still remains debatable whether the word ‘nano’ should be completely omitted from participant information sheets and IC forms for convenient (if perhaps unethical) reasons, or whether it should be mentioned and then simplified to make it understandable for trial participants.

We are of the opinion that the word ‘nano’ should not be omitted completely from participant information sheets and IC forms, especially if it has been used in grant applications, investigator’s brochure, trial protocol and documents submitted to the regulatory and ethical oversight authorities. To disclose the nano nature of a trial to everyone involved except trial participants would normally be unethical [24]. Furthermore, it is critical that all the risks, uncertainty and ignorance related to the nanoformulation being investigated in FIH trial are discussed in detail, and (as in all FIH trials) it is made clear that participants are unlikely to benefit from their participation but the knowledge gained may have significant scientific and social value, so that participants as well as ethics committees get complete information on potential risks and benefits. Otherwise, there is a danger of selective and convenient use of ‘nano’ terminology when it serves a beneficial purpose such as procuring grants and publishing results in prominent journals, but withholding it from the trial participants, regulatory authorities and ethics committees.

Most nanomedicine is being developed and licensed for cancer chemotherapy, and such products are always tested on patient groups who are terminally ill and who have exhausted all other proven treatment options. Cancer chemotherapy often induces many side effects and does not improve patients’ survival beyond a certain limit. In this context, nanotechnology can play a significant role but ‘nano’ should not be presented as ‘lesser evil’ as compared to standard chemotherapy. Nano might indeed reduce chemotherapy related toxicity but in FIH trials, it also has high potential to cause harm to the participants owing to

limited reliability of animal models and preclinical data based on which such trials are initiated in humans [26]. Nanomedicinal products achieve better targeting due to their nano size, penetrability into deep tissue spaces and transport across biological barriers. They also improve drug concentration at desired sites by altering pharmacodynamic properties. Targeted drug delivery reduces unwanted side effects but certain characteristics of nanoparticles can also produce new and unanticipated side effects. There is a thin line between beneficial aspects of nanoformulations and the toxicities they can produce especially when the product is being tested in FIH trials and it is essential to be open and honest about both these aspects in participant information sheets rather than only highlighting improved targeting as a potential benefit. The suggestion of giving a nanomedicinal product a neutral name (aspirin vs acetyl salicylic acid) might work to reduce fear associated with nanotechnology, but it would only be correct to do so after a drug has been licensed and robust post marketing surveillance over many years has proved its safety and efficacy. This is not the case for most nanomedicinal products at the moment. The earliest licensed nanomedicinal products have been now around for about 20 years but most products under translational research are very recent and there is limited safety as well as efficacy data available for them.

Finally, participant information sheets and informed consent forms are sources of scientific information that are based on peer reviewed evidence, reviewed by the drug regulatory authorities and ethics committees and provided by the enrolling physician to the participant. Patients often tend to trust their physicians and these trial related documents should also be trustworthy in terms of its completeness and correctness. As pointed out by one of our respondents, there is plenty of information accessible via the internet but its reliability and accuracy is questionable [27] unless it is published in peer reviewed scientific journals. Not many members of the public or patients have access to such journals and are more likely to receive distorted information from other non-peer reviewed sources. Even if they receive

scientifically correct information, interpretation of this information will also influence their decision making. Hence the accuracy, transparency and understandability of participant information sheets and informed consent are crucial and should not be compromised [13, 28]. This is indeed an opportunity for the scientists and investigators to ‘inform’ and ‘educate’ the potential trial participant about nanomedicine and empower them to make informed choices.

CONCLUSION

One of our respondents rightly referred to dilemma of use of ‘nano’ terminology in trial related documents as ‘starting one’s journey with left foot forward’. It is challenging to achieve the necessary balance between providing correct information and making it understandable, describing all the risks and benefits, and not give false hopes or overemphasize the harms and the risks. Each participant is different, their attitude, values and experience with clinical research are different and their personality is unique which will influence how they receive the information and the way they make a decision. The recruiting physicians need to be aware of these factors but the decision regarding whether to include terminology ‘nano’ in participant information sheets and IC forms should not be based on such individual traits of either the participant or the researcher. These documents need to have consistent, clear and honest communication regarding study design and investigational product. We believe that total exclusion or underplaying ‘nano’ for any reasons is dangerous and will threaten the trust of the public in science, technology and clinical research enterprise.

Scientists and investigators have a significant role to play in public engagement and science communication but there is only little that they can achieve on their own. They need to receive the necessary support from policy makers, funding agencies, drug regulatory authorities, ethics oversight, media professionals and general public to be able to carry out translational research without compromising on either research integrity or the safety of trial participants.

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Chapter 6

Stakeholder views on participant selection for first-in-human trials in cancer nanomedicine.

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ABSTRACT

Background Participant selection for first-in-human (FIH) trials involves complex decisions. The trial design makes it unlikely that participants will receive clinically relevant therapeutic benefit, but they are likely to experience risks of various magnitudes and types. The aim of the present paper was to describe and discuss the views of investigators and ethics committee members about the choice of trial participants for FIH trials in cancer nanomedicine.

Methods We drew insights from an exploratory qualitative study involving thematic analysis of 46 in-depth interviews with key stakeholders in Europe and North America involved in FIH nanomedicine trials. The present work draws on subset of 21 interviews with investigators and ethics committee members who have either conducted or reviewed a FIH cancer nanomedicine trial or are planning one.

Results Investigators and ethics committee members are aware of the ethical standards for recruiting patients with end-stage cancer into FIH trials, but they nonetheless questioned the practice and provided reasons against it.

Conclusions Although it is a standard and ethically accepted practice to include patients with end-stage cancer and no treatment options into FIH trials of investigational chemotherapeutic molecules, doing so can threaten the validity and generalizability of the trials, thereby weakening translational research. Another possibility is to stratify and include patients with less-advanced disease who demonstrate certain biomarkers or cancer genotypes and who have a disease profile similar to that tested in preclinical studies. The latter approach could be a step toward personalized medical research and targeted drug development. Such a patient selection approach requires multi-stakeholder discussion to reach scientific and ethics consensus.

Key Words First-in-human trials, trial participant selection, nanomedicine, qualitative research, empirical ethics

BACKGROUND

First-in-human (FIH) trials are crucial in translational research for experimental clinical applications, but they also pose the highest level of uncertainty with respect to potential risks to trial participants [1]. That uncertainty is attributed to the limited validity and reliability of preclinical research [2,3], to questions concerning the appropriateness of animal models [4], and to the lack of clarity about the mechanism of action of investigational products [5]. The goal of FIH trials is to gather information about the mechanism of action, to study the toxicity and safety profile, and to determine a safe and tolerable dose in humans, which will be the starting dose for further clinical trials in which the efficiency of the intervention is tested [6]. The dose-escalation design of FIH trials makes it highly unlikely that patients participating in such trials will receive clinically relevant therapeutic benefit, at least in the earliest cohorts testing low doses of the experimental molecules [7]. Trial participants are likely to experience side effects and harms of various types, magnitudes, and probability [8]. Some of the harms can be predicted from preclinical animal data. However, data from animal models cannot be reliably extrapolated to human beings, and substantial uncertainty and ignorance persists in assessments of the risks of FIH trials [9].

Compared with later-stage trials, FIH trials often involve fewer trial participants, thus reducing the number of individuals who could be harmed [6]. But if the participants selected for such trials are inappropriate, translational research is harmed in two ways: First, individual participants, even though few in number, are harmed. Second, human and financial resources are consumed in conducting trials that do not generate valid, reliable, and generalizable scientific knowledge that can guide further translational research or necessitate additional preclinical research [6,10].

The literature on participant selection for FIH trials mainly discusses 3 different categories of trial participants: healthy volunteers; patients with stable disease on standard

therapy, but who suffer nonetheless; and patients with terminal illness who no longer have any standard therapy options [11]. Researchers working with novel medical technology such as gene transfer and regenerative medicine have pointed out another category of potential FIH trial participants: individuals who are currently asymptomatic carriers of certain genetic or degenerative conditions that will manifest as a disease in future [12]. Participants in FIH trial are vulnerable for various reasons: therapeutic misconception [13–15]; undue hope and optimism that the investigational product will improve their health, or at least their quality of life [16]; perceived pressure to accept what their treating physician feels is good for them; and inadequate appreciation of unlikely benefits but likely harms [11]. The choice of trial participants for FIH trials involving cutting-edge medical technology such as gene transfer, regenerative medicine, cell-based interventions, and nanomedicine is further influenced by the novelty of the intervention under investigation, the limited reliability of disease models in animals [17], and the huge hype and hope that such technologies generate in the minds of patients and the general public [18]. The hype and hope make trial participants further prone to succumbing to the therapeutic misconception and underestimating the risks and likelihood of harms.

The choice of trial participants for FIH trials involves a delicate balance between the requirements of the study protocol and design (protocol-driven factors) and participant-related factors from the perspective of patients and healthy volunteers. A significant body of literature has explored the motivations, hopes, and expectations of healthy volunteers and patients who participate in various clinical trials, including FIH trials [19–25]. Patient-related factors influencing the decision about whether to participate in FIH trials include unmet need for treatment options, lived illness experience, suffering and impact on quality of life, willingness to accept higher risks in the hope that the experimental treatment might provide at least symptom relief if not cure, and familiarity with and understanding of clinical trials and

investigational molecules. We believe that the patient perspective on trial participation merits its own investigation. Our research project has two separate arms: one focusing on patient perspectives and the other on expert stakeholders. In the present work, we specifically explore the perspectives of expert stakeholders about the selection of FIH trial participants.

The goal of our paper is to summarize and discuss the views and thought process of principal investigators (PIs) and ethics committee members (ECMs) about the "ideal or most appropriate" trial participants for their FIH trials in nanomedicine. We are aware that FIH trials constitute a heterogeneous group of trials and encompass a large spectrum of scenarios, from FIH testing of a slight modification of an already licensed drug at one end, to the testing of a completely novel investigational molecule based on cutting-edge technology that has never before been tested in humans at the other. For the purpose of the present work, we focus on the latter end of the spectrum, where novel investigational products or molecules are being tested in humans for the very first time, and safety or toxicity data for humans from prior experience with other similar products are unavailable or limited.

We used medical applications of nanotechnology as a prototype for our investigation into the challenges of clinical translation of cutting-edge medical technology. Because of their size or unique physical and chemical properties (or both), nanomedicines allow for the development of highly sensitive and specific diagnostic tools that could facilitate early disease detection and improved monitoring of disease progression. They provide efficient drug delivery mechanisms and platforms, with better targeting to disease lesions and delivery of higher concentrations of drugs at desired sites, thus improving drug efficiency and reducing side effects [26,27]. Though nanotechnology-based diagnostic and therapeutic interventions are expected to revolutionize the understanding of disease mechanisms and the ability to treat or cure the diseases, significant concerns and uncertainties also pertain to the risks and harms caused by nanoparticles to humans and the environment [28]. That tension between immense

hope and hype about the potential of nanotechnology in medicine, and the fear and reluctance attributable to its feared toxicity makes nanotechnology an interesting case study, especially to discuss the challenges it poses in translational research.

Here, we describe and discuss insights from a subset of 21 of 46 in-depth interviews with translational nanomedicine stakeholders based in Europe and North America who have either conducted or evaluated a FIH trial or who are planning one in the near future. Stakeholders discussed mainly nanomedicine-based cancer chemotherapeutic drugs because most of the approved nanomedicines are anticancer agents. Although there is a vast body of literature on participant selection for FIH trials in general and cancer trials in particular, we are not aware of any other empirical investigation in which trial participants for FIH cancer nanomedicine trials have been discussed. We believe that the present work will shed further light on the concerns expressed by scholars working on the ethics of nanomedicine and physicians caring for cancer patients. It will in particular help to clarify the reasons and arguments stakeholders use to justify their choice of FIH trial participants.

METHODS

For this exploratory qualitative research, we used in-depth interviews to elicit the views and experiences of stakeholders involved in FIH trials in nanomedicine in Europe and North America. In-depth interviews were facilitated with a semi-structured list of open-ended questions and focused on understanding the various challenges (including ethical challenges) faced by the stakeholders of translational nanomedicine. Interviews allowed us to build a dialogue with the expert stakeholders and provided them the necessary space to highlight arguments and experiences that they found pertinent and worthy of discussion. All the respondents discussed financial, ethical, patent-related, and regulatory challenges that are applicable to translational research in any cutting-edge medical technology [29]. But a subset of the respondents who had either conducted or were planning to conduct FIH nanomedicine cancer trials reflected extensively on specific challenges they faced while justifying their

preferred choice of trial participants either to themselves or to the ethics committee. The present work focuses on the reflections of those stakeholders and on the specific dilemmas they faced in the choice of trial participants while ensuring scientifically and ethically sound study design and the generalizability of knowledge gained.

Respondents

We interviewed scientists affiliated with universities, academic centres, small- and medium-size enterprises, and large pharmaceutical companies; physicians and PIs of trials; ECMs or members of institutional review boards; representatives of drug regulatory authorities, patient advocacy groups, clinical research organizations, and venture capitalists. Those roles are not necessarily mutually exclusive. The heterogeneity of the respondents allowed us to understand the challenges of translational nanomedicine from the perspectives of the various stakeholders involved and the specific roles they play in the process, but it also posed a few specific methodological challenges such as theoretical saturation and quantifying responses according to the roles the respondents played. Some of those challenges are described in subsections that follow. The present work draws on a subset of 21 of the 46 respondents and includes the experiences and opinions of scientists, physicians, PIs (collectively referred to as "investigators") and ECMs or institutional review board members who had either conducted or evaluated a FIH nanomedicine trial or were planning one in the near future. Their profiles are summarized in Table I. The remaining 25 respondents did not have specific comments or reflections on choosing trial participants either because they had not considered the topic and were still focused on preclinical research or their role in translational research did not include having to choose participants for FIH trials.

Interview Guide

An extensive literature review helped us to create a list of open-ended questions for the interviews with key stakeholders. This semi-structured interview guide steered the discussion and allowed respondents to describe salient issues, experiences, and thoughts. Stakeholders

involved in translational research were expected to have varied professional backgrounds and to play a specific role; hence the interview guide had to be flexible and to address questions relevant to the role the stakeholder played in a particular trial. The guide thus had to be adapted while interviewing an expert in nanotechnology–nanomedicine patent law, who might not have had specific views about participant selection, but who would highlight challenges linked to patent evaluation and granting, which are linked to the interests of the investors or venture capitalists and hence connected with the ability of an investigator to generate financial resource to move from preclinical research to early human trials.

The interview guide was pilot-tested with 3 colleagues experienced in qualitative research and the ethics of medical technology. The pilot interviews were excluded from the final data set. The interview guides were approved by the local ethics committee and are published as supplementary material to one of our published articles http://www.sciencedirect.com/science/article/pii/S1549963415006218 (subscription required).

Interviews and Transcription

All stakeholders were interviewed in English by PS between October 2013 and November 2014—in person whenever possible or over the telephone—using purposive maximum variation sampling [19]. Oral informed consent was obtained from all participants before the interview, and permission was asked to record the conversation on an audio device. The ways in which the confidentiality and anonymity of their views would be ensured were explained. Interviewees could refuse to answer any question or could ask for the recording to be stopped for particular sections of the interview. Interview durations ranged between 20 minutes and 60 minutes, with the average time being 50 minutes. We continued interviewing stakeholders until data saturation was reached (a stage at which the research team was convinced that no new themes relevant to the aims of the study were emerging with additional interviews) [30]. Given the heterogeneity of the sample, theoretical saturation was reached at varying time points for the various themes under discussion; timing depended on how many of our

stakeholders had views on the particular topic. Together with research assistants, PS transcribed all interviews verbatim and in full; PS also checked all interviews against the audio recording and sent the transcripts to respondents to check the contents and the accuracy of technical details, as well as to solicit additional thoughts or suggestions.

Data Analysis

At the beginning of data collection, PS simultaneously undertook a preliminary data analysis, the insights from which were included in subsequent interviews. She used the qualitative analysis software MAXQDA (Verbi GmbH, Berlin, Germany) to carry out deductive data coding. DMS undertook a similar exercise manually. The resulting codes were built into themes and discussed using manual and software-assisted data analysis until the research team reached agreement.

The research team extensively discussed the advantages and disadvantages of deductive and inductive data coding as an approach for the data analysis, but eventually agreed on deductive data coding in light of time and funding constraints. For the present work, the goal was to discuss the range of views and experiences rather than the frequency of similar views. So, instead of quantifying the results, they are therefore described in general terms—for example, “a few,” “some,” “many,” “all.”

Ethics Approval

The ethics commission of northwest and central Switzerland (Ethikkommission Nordwest und Zentralschweiz) approved the research project and the interview guide in January 2013.

RESULTS

Of 46 respondents, 25 were working on various stages and aspects of clinical translation in nanomedicine such as bench research, animal experiments, toxicity assessment, and manufacturing of the required investigational compound under the conditions of good manufacturing practice; the remaining 21 had direct involvement with FIH trials in various capacities (investigator, trial physician, trial coordinator, ethics committee member,

representative of a drug regulatory authority). The FIH trials were focused on nanotechnology-based drug delivery platforms in cancer, diabetes, immunologic disorders, cardiovascular disease, and infectious disease.

With those 21 stakeholders, we explored views about the "ideal or most appropriate" trial participant for their FIH trial in nanomedicine and the underlying reasons for their choice. All 21 stakeholders advocated for a case-by-case assessment of participant selection for FIH trials with various interventions or experimental molecule and referred to various ethics guidelines such as Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/), regulatory guidelines from the U.S. Food and Drug Administration for the investigation of new drugs (http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm) and the European Medicines Agency (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000564.jsp&mid=WC0b01ac05806403e0), and clinical research guidelines such as the *Guideline for Good Clinical Practice* from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf), which provide guidance on participant selection and clear formulas for calculation of the starting dose for FIH trials.

Because most nanomedicines have been developed and approved for cancer treatment, the focus of the discussions was on nanomedicine-based cancer trials, but respondents also mentioned other trials involving stem-cell therapy and gene transfer when making their arguments. We describe our results using select quotations from the subset of 21 interviews to highlight most important aspects of the theme under discussion. Our aim was to demonstrate the spectrum of arguments rather than to quantify how often a particular argument was used.

To protect the confidentiality and anonymity of respondents (Table I), we tag each quotation with a respondent number (R1, R2, ...), followed by their role.

"Ideal" Participants Might Not Always Be the Most Ethical Choice

All stakeholders were aware that most FIH cancer trials include patients with no treatment options, per the international ethics standards.

> You will never, *never* accept a study that is a healthy volunteer study with a chemotherapeutic agent. You test it in tumours, immunocompromised mice with tumours, then in patients who are extremely sick with metastasis, tumours which cannot be cured by any other existing drug. You try it first on such patients and then you slowly go backwards to less sick patients.- **R6, ECM**

> We ideally would have a patient who is partially previously treated, because that is also logical. It is also ethical that you should first give the patient a well-known treatment—the standard of care so to say—and if the first and the second line is not working anymore, only at that point, it is ethical to go on continuing with something novel, either for the sake of science or for it might really have an added value in that specific patient.
> **- R21, scientist planning a FIH nanomedicine trial**

Some stakeholders highlighted the constraints and challenges of including only the sickest patients in FIH trials.

> [They have had] a lot of other treatments before. They often are not in a good condition. They have very limited life expectancy. These are patients who always have problems—lot of the adverse events and serious adverse events. These are not randomized controlled trials, so many of these adverse events are attributed to the disease itself and not to the drug. So this is not the best way. But when a patient has treatment options with proven benefit, it is not ethical

to use a drug where you don't know first the dose, the efficacy, and it is debatable if patient will have any benefit. This is why most of the new drugs in oncology are tested on dying patients. It is not ideal for the drug, but it is not ethical to give patients a treatment which might be inferior to an existing treatment. - **R12, physician and PI who conducted a FIH nanomedicine trial**

Other stakeholders argued that the ideal participants are actually newly diagnosed cancer patients, or even better, patients with specific mutations or those who are known to have particular biomarkers that can be detected using imaging techniques.

Ideal patients are the new patients that get diagnosed with the tumour because they have no prior treatment and no resistance. Those will not be allowed to join such trials of course. You have to do your trials in terminal-stage cancer patients, after which you can decide that it is safe enough to apply this technology and then you need to find a certain group of patients that will participate in the phase II trials when the efficacy will be studied. Even at that stage, you won't get new patients but pre-treated patients. But there you can try to get some cure. It is logical especially in phase I trials where we only focus on the risks and toxicity, tolerable dose, etc. But in the next phases, you would like to treat the right patients that could benefit from this particular application.

- R8, scientist planning a FIH nanomedicine trial

Bear in mind that we have stage IV patients with metastasis all over. So anyway it will be palliative treatment that they will take. In that context, sometimes we can have a strong rationale that these patients might benefit from this new drug. Let's say we have patient with stage IV lung cancer with a particular molecular marker. So if we know that these patients do not respond to any other treatment, and that we have found in pre-clinical study that, in cell

> model and in animal models, tumours with these specific mutations respond to the treatment that we want to test, we have a rationale that may be strong enough to go in naïve patients [treatment-naïve patients whose cancers have been diagnosed late]. - **R23, trial coordinator from a large pharmaceutical company**

Choosing treatment-naïve, recently diagnosed cancer patients for FIH trials was perceived as ethically challenging by all stakeholders, but they also pointed out the importance of other factors such as type of cancer, availability of standard therapy, prognosis, and time available to intervene.

> We often discuss whether the knowledge you want to gain requires a study in patients with end-stage disease or [whether] you can test it on patients who are not that sick. It is a very difficult decision. What you don't want is to give false hope to patients with end-stage disease. You can also do part of the study in newly diagnosed patients or patients in between on the spectrum of disease progression, depending on life expectancy of the patient with his or her particular type of cancer. If we use newly diagnosed patients to study toxicity, one must assess if they have a possibility of trying other existing established therapies three or four weeks later or they have to start immediately with the accepted standard therapy. If we know that the experimental therapy under investigation is not going to negatively influence the standard established therapy after a few weeks. If here is no cross-reaction, or resistance, and we can have that time gap, it can be a good case. - **R9, ECM**

Another argument for testing new drugs in relatively healthier cancer patients is to better assess side effects and toxicity.

> In the first- or second-line treatments, it depends on the disease but when the patient is still fit and still has higher chance to benefit from the drug. On every drug, there is a ratio between the efficacy and side effects. And if you go to the patients, who are in worse physical condition, the side effects will be more pronounced than the efficacy. This will not be the case if the patients are fitter and if you treat the patients during the first or second line. - **R12, physician and PI who conducted a FIH nanomedicine trial**

Stakeholders also noted the specific character of particular cancers: some have very rapid progression and do not have many treatment options in the first place.

> It depends on the disease, actually. For example, non-small-cell lung cancers, it is matter of debate. We know that non-small-cell lung cancer is a disease with rapid progress, and patients deteriorate quite quickly and only about 60 per cent to 70 per cent of all patients receiving first-line therapy get the second-line therapy. This will also be the case if you treat these patients in FIH trial with a new drug. And there will be one third or more of these patients not receiving the established first-line therapy. If you have a disease where most of the patients are dead after 12 months, this is quite different than a disease where you have time. For example, low malignant lymphoma when you have time in years. It might be the case here to test the new drug in first line, so you can rescue them in the second line with an established treatment. - **R31, PI planning a FIH nanomedicine trial**

First-in-human trials are typically toxicity and dose-finding studies. Another factor that influences participant selection for FIH trials is the burden of risk for participants and, particularly, how long they might have to live with those risks.

> Well, “ideal” is a difficult term in this context because what they usually want for these trials are patients who will not be bothered by the long-term risks because they will not survive long. So if you want to know the ideal oncology patients to participate in this kind of trials, it is the patient who is certain that there is no treatment anymore but who is in a reasonably good condition. You don’t want to burden someone who is really at the end of his life and in a bad health condition. - **R22, physician and ECM**

Challenging the Standard Design of FIH Trials

Some of our respondents criticized the traditional dose-escalation model of FIH trials, arguing that it might not be the best model for trials involving novel medical technology such as nanomedicine, stem-cell interventions, or gene transfer. One of the reasons for that stance was a lack of clarity concerning the dose–response relationship. Another concern was whether it was ethical to use the standard starting dose calculation from the animal models (as elaborated next, in discussing the case of stem-cell injection into a spinal cord lesion).

> But the problem is [pause] to do a FIH study with ineffective dosage which provides him absolutely no benefit and makes him more desperate. One actual example is the vaccination against the Ebola virus. I don’t think they did a classical first-in-man study; they probably started with the expected immunogenic dose and looked if it works, if antibodies are generated. They don’t challenge them with a dose which is one hundred times smaller than what you would expect to make an immune reaction. The classical first-in-man study is excellent with new drugs, but in these situations like the spinal cord lesion it is not feasible unless you believe that even a very small amount of these stem cells can create a malignant tumour. - **R46 physician and ECM**

DISCUSSION AND CONCLUSIONS

The goal of FIH trials is to produce valid, reliable, and generalizable scientific knowledge that could guide further translational research [10]. Ethics evaluation of such trials often hinges on balancing harms to the trial participants against the social and scientific value of research, rather than on a traditional risk–benefit evaluation for the trial participants [31]. Scholarly discussion about involving patients with end-stage disease and no proven treatment options in FIH trials has focused on the vulnerability of such patients, the high likelihood of therapeutic misconception, the problems of information disclosure, and participation in decision-making [11].

Our results, however, highlight a significant conflict experienced by investigators and ECMs between doing what good ethics practice mandates (that is, enrolling only patients with end-stage disease and no treatment options in FIH trials, thus protecting other patients against unjustified and uncertain harms of exposure to unproven interventions) and what good scientific practice requires (that is, selecting less-ill patients for such trials so that results could guide further translational research). Abiding by ethics norms in terms of acceptable risk–benefit assessment for individual patients in turn adversely affects the clinical trial's validity and reliability. Patients with advanced disease and no treatment options are fragile and weak. Enrolling them in FIH trials to assess an investigational product's safety and toxicity profile increases their risk of experiencing severe side effects and adverse reactions. Because most FIH studies are not randomized controlled trials and do not involve blinding, many of the adverse events patients experience in such trials might not be accurately attributed to the investigational drug but instead to the underlying disease. That possibility will significantly weaken the goal of gaining scientific knowledge, either necessitating further preclinical testing or guiding later clinical research and potentially harming more patients who will be eventually tested with the same product in phase II/III trials.

Some researchers have argued for a modification of dose escalation FIH trials, such that most trial participants will receive a potentially effective dose[11]. That change will be beneficial only if the investigational product indeed turns out to be efficacious, a finding that is not often the case in many FIH trials. Large numbers of investigational products fail to demonstrate efficacy in humans, which is required for a product license[32]. If the investigational product has serious side effects, then the trial participants in any such modified FIH trials are also likely to experience more serious side effects proportional to the higher dose received, and thus more patients than necessary will be exposed to the harms.

Others have argued for more rigorous preclinical research using appropriate animal models, and bringing randomization and blinding into preclinical animal experiments to achieve higher methodologic and scientific rigour so that potential harms in humans can be better predicted[10].

Are there ways to move trial designs in terms of patient recruitment from terminally ill patients to other patients whose disease is not so advanced? That latter group of patients could be included in FIH trials with new drugs for a short period of time and could later be rescued by proven standard therapy provided there is no drug interaction or resistance related to their trial participation.

Given improved understanding and assessment of biomarkers and cancer genotyping, and advances in imaging techniques, it will be worthwhile to stratify patients further, thus choosing for particular FIH trial only those who express a certain biomarker or who demonstrate conditions similar to those tested in preclinical animal models, regardless of how severe their disease is at the time of trial participation. Patient recruitment of that type could be a step toward personalized clinical research in a limited sense. In cancer chemotherapy using liposomes as a nanomedicine drug delivery platform, for example, it might be possible to preselect patients who demonstrate enhanced permeation and retention of liposomal

nanoparticles on imaging studies. Many liposomal chemotherapeutic formulations use the enhanced permeation and retention effect as the main passive mechanism of drug delivery to cancerous lesions [33]. The nanoscale size of liposomes filled with active licensed chemotherapeutic drugs allows for their extravasation from leaky tumour vasculature into the tissue spaces and tumour stroma. The active chemotherapeutic compound encased within is then released, thus concentrating the drug locally, improving the efficacy of cellular lysis and minimizing toxicity to surrounding healthy tissue. Not all patients have tumour vasculature that is leaky enough to allow for the distribution of a sufficient concentration of liposomes into the tumours, but patients who have sufficiently leaky tumour vasculature can be identified using certain imaging techniques. Although that approach will involve more costs because of the inclusion of diagnostic and prognostic imaging endpoints in such FIH trials, researchers will be able to choose appropriate trial participants in whom the drug can be concentrated locally and to produce a reliable scientific understanding of the mechanism of action and toxicity of the investigational product and a preliminary assessment of efficacy, if any. Furthermore, other patients (with no demonstrated enhanced permeation and retention effect) who are unlikely to benefit from the liposomal investigational product will be protected against unnecessary harms related to their trial participation by exclusion at the outset of the trial.

Finally, a discussion about appropriate participant selection is incomplete without meaningful engagement with patient populations or patient advocates in trial planning, evaluation, and decision-making. The framework for such engagement has to be flexible, proportionate in terms of risks and benefits, and transparent. However, it is not always easy to define who the appropriate representatives of patient populations are [34] and whether they could objectively assess potential harms and benefits for each trial. The literature describes the role of patient advocates in advocacy for fund mobilization, communication with potential

trial participants, support for newly diagnosed patients, and informing policy and oversight [35,36], and yet it is debatable what role—if any—they should play in ethics evaluations of FIH trials of cutting-edge medical technologies. Our research project focused on professional stakeholders and did not receive input from patients with the exception of 1 representative from a patient advocacy group. Further research into understanding what meaningful patient engagement could contribute to translational research will be immensely valuable.

We are aware of a few methodology limitations related to the purposive sampling technique in the present study. Although the results of this exploratory study have limited generalizability, they raise important questions about appropriate trial participants for FIH trials in cancer nanomedicine, thus generating an important debate. In-depth interviews also allowed us to gain insight into the reasons for the feeling on the part of key stakeholders of FIH nanomedicine trials that patients with advanced disease might not be the appropriate participants in early translational research in humans, even though such participants are justified and recommended by ethics guidelines. Further studies with larger and homogeneous study populations will increase the evidence base and help to determine whether these dilemmas about participant selection in FIH cancer nanomedicine trials are also relevant to any FIH trials with cancer patients regardless of whether they involve cutting-edge medical technology.

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nanomedicine: a qualitative study. *Nanomedicine* 2016;12:893–900.

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TABLE I Profile of expert stakeholders [a]

Affiliation	
Academic researcher	20
Subject matter expert	8
Large pharmaceutical industry	6
Ethics expert or IRB member	6
Drug regulator	2
Venture capitalist	1
Patient advocacy group	1
Industry consultant	2
TOTAL	46
Experience of FIH trials in nanomedicine	
Trial completed	11
Advanced preclinical and planning work	10
TOTAL	21
Targeted disease	
Cancer	9
Diabetes	2
Immunologic	5
Cardiovascular	1
Infectious	4
TOTAL	21
Main drug delivery platform	
Liposomes	8
Gold nanoparticles	3
Silver nanoparticles	1
Polymer micelles	2
SPIONs	2
siRNA	1
Silica multistage vectors	1
Others	3
TOTAL	21

[a] Descriptions of the countries in which they work and the roles they perform were intentionally withheld to ensure anonymity. Completed FIH trials in nanomedicine are few in number, and so with the information about the disease target, drug delivery platform, and country, the identity of the respondents could be easily deduced.

IRB = institutional research board; FIH = first-in-humans; SPIONs = superparamagnetic iron oxide nanoparticles; siRNA = small interfering RNA.

Chapter 7

Prioritizing healthcare workers for Ebola treatment: Treating those at greatest risk to confer greatest benefit

Priya Satalkar, Bernice S. Elger, David M. Shaw

Satalkar P, Elger B S, and Shaw D. (2015) Prioritizing Healthcare Workers for Ebola Treatment: Treating Those at Greatest Risk to Confer Greatest Benefit. Developing World Bioethics. 15(2): 59-67.

Abstract

The Ebola epidemic in Western Africa has highlighted issues related to weak health systems, the politics of drug and vaccine development and the need for transparent and ethical criteria for use of scarce local and global resources during public health emergency. In this paper we explore two key themes. First, we argue that independent of any use of experimental drugs or vaccine interventions, simultaneous implementation of proven public health principles, community engagement and culturally sensitive communication are critical as these measures represent the most cost-effective and fair utilization of available resources. Second, we attempt to clarify the ethical issues related to use of scarce experimental drugs or vaccines and explore in detail the most critical ethical question related to Ebola drug or vaccine distribution in the current outbreak: who among those infected or at risk should be prioritized to receive any new experimental drugs or vaccines? We conclude that healthcare workers should be prioritized for these experimental interventions, for a variety of reasons.

Keywords

Africa, bioethics, clinical studies, community engagement, resource allocation, Ebola, disease surveillance.

Introduction

The current Ebola epidemic started with the diagnosis of a two year old boy in Guinea in December 2013[1]. By December 31, 2014, cases have been reported in four countries (Guinea, Liberia, Sierra Leone, Mali) and four other previously affected countries (Nigeria, Spain, the US and Senegal). There are 20,206 suspected and confirmed cases, and 7905 reported deaths. A total of 678 health care workers have been infected with 382 deaths[2]. The World Health Organization has described the epidemic unprecedented and estimates that it will continue to spread for another four to six months before it can be controlled, infecting as many as 20,000 people[3] [4]. This epidemic is unique due to the very high numbers of cases compared with all previous outbreaks[5], high infection rates amongst health care workers[6] and because it

[1] Lancet editorial. Ebola: a Failure of International Collective Action. *Lancet* 2014; 384: 637.

[2] World Health Organization (WHO). 2014. Ebola response road map: Situation report update, December 31, 2014. Geneva, Switzerland. . Available at: http://www.who.int/csr/disease/ebola/situation-reports/en/ [Accessed on 05 Jan 2015].

[3] World Health organization (WHO). 2014. Ebola response roadmap. Geneva, Switzerland. Available at: http://apps.who.int/iris/bitstream/10665/131596/1/EbolaResponseRoadmap.pdf?ua=1 [Accessed on 05 Jan 2015].

[4] Lancet editorial, *op. cit.* note 1.

[5] C. del Rio et al. Ebola Hemorrhagic Fever in 2014: The Tale of an Evolving Epidemic. *Ann Intern Med* 2014.

[6] World Health organization (WHO). 25 Aug 2014. Unprecedented number of medical staff infected with Ebola. Geneva, Switzerland. Available at: http://www.who.int/mediacentre/news/ebola/25-august-2014/en/ [Accessed on 05 Jan 2015].

has affected countries which do not have prior experience of and expertise in controlling Ebola outbreaks[7]. Fortunately, however, the overall fatality rate at the moment is about 39%, which is lower than in most of the previous outbreaks but the fatality rate among health care workers is 57%, which is a major concern given the limited health human resource in Ebola affected countries[8]. It might be thought that health care workers would have better overall health status, be diagnosed earlier and treated faster thus leading to better health outcomes. However, the most recent data reveals higher mortality rates among health care workers, which could be attributed to their exposure to a large number of patients while having limited personal protection, at least in the beginning of the epidemic. In previous Ebola outbreaks, amplified transmission has been documented in health care centers with approximately a quarter of all cases occurring in health care workers[9].

As in the past, transmission could be slowed and prevented by the basic principles of public health, such as exhaustive case and contact tracing, effective response to patients including supportive care, involving local communities while planning interventions, and robust infection control practices in health care settings and during burial procedures[10]. But there are many challenges in controlling this epidemic, including porous national borders with movement of people for work, fragile health care systems,

[7] C. del Rio, *op. cit.* Note 5, p 1.

[8] WHO, *op. cit.* Note 2, p 1.

[9] C. del Rio, *op. cit.* Note 5, p 1.

[10] T. R Frieden et al. Ebola 2014- New Challenges, New Global Response and Responsibility. *N ENGL J MED* 2014.

weak surveillance and diagnostic facilities, cultural beliefs and practices, and local communities' lack of trust in Western biomedicine and foreign health care workers[11]. The situation has been further complicated by delayed global support and response to the epidemic[12].

There are no licensed and approved treatments or vaccines against Ebola. The complexity and magnitude of the epidemic led the World Health Organization to reach a consensus that 'it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention[13]. The WHO also highlighted the need to start phase I clinical trials in healthy volunteers with candidate vaccines as quickly as possible, along with continuing compassionate use of unproven interventions in patients in emergency settings, provided the data concerning compassionate use is meticulously collected and analyzed[14]. The first phase I trial of a potential Ebola vaccine has already begun at the

[11] A. S. Fauci. Ebola- Underscoring the Global Disparities in Health Care Resources. *N ENGL J MEd* 2014.

[12] R. Anusumana. Ebola in Sierra Leone: a call for action.*Lancet* 2014.

[13] World Health Organization (WHO).12 August 2014. *Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD)*. Geneva, Switzerland: WHO. Available at: http://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/ [Accessed on 05 Jan 2015].

[14] World Health Organization (WHO). 2014. Ethical considerations for use of unregistered interventions for Ebola virus disease: Report of an advisory panel to WHO. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/130997/1/WHO_HIS_KER_GHE_14.1_eng.pdf [Accessed on 05 Jan 2015].

National Institutes for Health in Bethesda, US with 20 healthy volunteers[15], and another phase 1 trial in 60 healthy volunteers began in the UK in collaboration with Glaxo SmithKline and the NIH on 17th September[16]. Switzerland has initiated parallel trials of two candidate vaccines and aims to enroll 150 healthy volunteers[17] [18], while Mali has undertaken a similar trial with 40 healthy volunteers[19]. Use of limited doses of Zmapp, a combination of three monoclonal antibodies for seven patients including health care workers had fuelled much hope, hype and speculation concerning who should have access to this drug in case it is proved to be

[15] National Institutes of Health (NIH). 28 August 2014. *NIH to Launch Human Safety Study of Ebola Vaccine Candidate. Bethesda, Maryland.* Available at: http://www.nih.gov/news/health/aug2014/niaid-28.htm [Accessed on 05 Jan 2015].

[16] Reuters. 2014. *First UK volunteer gets experimental GSK Ebola shot in trial.* London. Available at: http://uk.reuters.com/article/2014/09/17/uk-health-ebola-vaccine-idUKKBN0HC17K20140917 [Accessed on 25 Nov 2014].

[17] ClinicalTrials.gov. 2014. VSV-ZEBOV Geneva Vaccine Trial. Available at: http://clinicaltrials.gov/ct2/show/NCT02287480?term=Ebola&cntry1=EU%3ACH&rank=1 [Accessed on 05 Jan 2015].

[18] ClinicalTrials.gov. 2014. A Clinical Trial on the Candidate Vaccine cAd3-EBOZ in Healthy Adults in Switzerland. Available at: http://clinicaltrials.gov/ct2/show/NCT02289027?term=Ebola&cntry1=EU%3ACH&rank=2 [Accessed on 05 Jan 2015].

[19] ClinicalTrials.gov. 2014. Phase 1 Trial of Ebola Vaccine in Mali. Available at: http://clinicaltrials.gov/ct2/show/NCT02267109?term=Ebola&cntry1=AF%3AML&rank=1 [Accessed on 05 Jan 2015].

efficacious[20]. The effectiveness of Zmapp in treating Ebola is not yet proven despite the recovery of two American health workers and one British health worker. These recoveries cannot be fully attributed to the drug alone, as all three of them received excellent supportive care in advanced intensive care settings and infectious disease isolation centers in the US and the UK respectively[21]. Furthermore, two other patients (a priest from Spain and a doctor in Liberia) who were also given Zmapp have died, making the known mortality rate for patients on Zmapp very similar to the normal mortality rate for this outbreak[22]. However, these deaths cannot be attributed to Zmapp being ineffective, as the drug was administered many days post-infection in both cases and some patient-related factors such as age could also have contributed to a more protracted disease course[23]. The latest results of a study where 18 macaques given Zmapp early in the course of infection were protected against a lethal dose of Ebola has again fuelled hope and anticipation of a 'magic bullet against Ebola' in the research community, among health care professionals and in communities affected by Ebola[24].

Even if some of the experimental drugs and vaccines are shown to be safe and efficacious based on expedited phase I trials, a number of issues

[20] T. W. Geisbert. Ebola Therapy Protects Severely Ill Monkeys. *Nature* 2014 doi:10.1038/nature13746; A. Rid & E. Emanuel. Ethical Considerations of Experimental Interventions in the Ebola Outbreak. *Lancet* 2014; DOI: 10.1016/S0140-6736(14)61315-5.

[21] A. Mullard. Experimental Ebola Drugs enter Limelight. Lancet;384:649.

[22] J.L.Goodman. Studying "Secret Serums"- Towards Safe , Effective Ebola Treatments. *N Engl J Med* 2014.

[23] A. Mullard, *op. cit.* note 21.

[24] T. W. Geisbert, op. cit. Note, 20.

related to available resources and capacity and ethical questions must be answered before making a decision to implement therapeutic or experimental interventions in countries worst affected by the epidemic. The drug or vaccine will not be a magic bullet to halt the epidemic, and will have to be coupled with basic principles of public health and epidemic control such as strengthening continuous disease surveillance systems including case and contact detection, case management, isolation and supportive care. In addition, resources must be invested in establishing diagnostic facilities and building the capacity of local health care systems to detect and control future outbreaks before they turn into epidemics[25]. Such interventions require sustained and focused investment not only in terms of monetary resources but also in building human resource, technical competences, political willpower and global cooperation[26].

In this paper we first argue that, independent of any use of experimental drugs, simultaneous implementation of proven public health principles, community engagement and culturally sensitive communication are critical in the current and any future Ebola epidemics as these measures represent the most cost-effective and fair utilization of available resources. This might sound obvious and may not appear to be an ethically contentious issue. Yet it is critical that the limited public health resources available in West Africa are used judiciously in the current epidemic for disease surveillance, provision of care and the phase II vaccine and drug trials planned for early next year. Second, we attempt to clarify ethical issues

[25] T. R Frieden et al, *op.cit.* note, 10, p.2.

[26] A. Rid & E. Emanuel. Ethical Considerations of Experimental Interventions in the Ebola Outbreak. *Lancet* 2014; DOI: 10.1016/S0140-6736(14)61315-5.

related to experimental treatment as even if such experimental drugs or vaccines can realistically be produced only in very small quantities during the current epidemic, will play an important role in halting the epidemics probably only in future Ebola outbreaks. We therefore aim to highlight the strengths and challenges of both these intervention strategies and lay out the limitations of each. We explore in detail the most critical ethical question related to Ebola drug/vaccine distribution in the current outbreak: who amongst those who are infected with or at high risk of acquiring Ebola should be prioritized to receive an experimental vaccine or drugs during phase I/II trials in countries affected by Ebola?

Public health measures helped curtail previous outbreaks

Since the first documented Ebola cases in 1976, the world has seen several sporadic outbreaks[27]. Compared with the current epidemic, all the previous outbreaks have been smaller in scale in terms of both the number of cases reported and the geographic spread of the disease. The mortality rate has varied from 25% to 90%[28]. All of these epidemics were controlled in the absence of a vaccine or drug with proven public health intervention. These intervention measures include early case detection and isolation, meticulous contact tracing, observing patients' contacts for signs of illness during the disease incubation period, providing supportive care to patients and their contacts and implementing rigorous infection control procedures observed in health care settings[29].

[27] C. del Rio et.al, *op. cit.* note 5, p.2.

[28] A. S. Fauci, *op.cit.* note 11, p.1.

[29] T.R. Freiden et.al, op.cit. note 10, p.2; A.Rid &E.Emmanuel, op.cit. note, 26, p.1.

A health care system adequately staffed with trained health professionals and stocked with an adequate supply of protective equipment such as overall aprons, masks, gloves and disinfection materials is critical in controlling an Ebola outbreak. But countries affected by the current outbreak in Western Africa (Sierra Leone, Liberia, and Guinea) face a number of challenges. For example, these are some of the world's poorest countries, and they have been affected by long periods of political conflict[30]. They have very poor health infrastructure, diagnostic facilities and reference labs such as P4 biosafety labs which are required to handle highly infectious pathogens such as Ebola[31]. They have very low physician-to-patient and nurse-to-patient ratios[32], meaning communities' health needs are not adequately met even in the absence of an Ebola epidemic. Most people rely on informal health care providers and traditional healers to resolve most health issues[33]. Because nonspecific early symptoms of Ebola mimic those of other common conditions in the area such as malaria and typhoid, most cases take some time to be formally diagnosed in the health care system, having already increased the risk of disease transmission to family members and other community contacts[34]. Ongoing routine disease surveillance systems which could pick up such outbreak at the earliest are practically absent[35]. The population in these parts of Western Africa has grown

[30] A.S.Fauci, *op.cit.* note 11, p.2.

[31] R.A.Ansumana, et.al, *op.cit.* note 12, p. 303.

[32] C. del Rio et.al, *op. cit.* note 5, p.1.

[33] Lancet editorial, *op.cit.* note 1, p.637.

[34] A.S.Fauci, *op.cit.* note 11, p.2.

[35] C. del Rio et.al, *op. cit.* note 5, p.1.

significantly in the last 4 decades and with increased human movement and migration[36], large slum settlements and efforts to collect bush meat for sustenance have created an optimal environment for increased contact between humans and wild reserves of the virus and for circulation of the virus within the human population[37].

Even though public health measures were able to stop previous Ebola epidemics, it is impossible to rely solely on these principles as a means to end the current epidemic, for two main reasons. First the epidemic has matured and has already spread to six countries, though Nigeria and Senegal are now declared free of Ebola. Second, building health care systems and disease surveillance abilities takes time and so does building the trust of local communities in formal health care and Western biomedicine. Efforts have already been made to set up Ebola treatment centers in affected communities but these are overrun by the people who require health care[38]. The high infection and fatality rates among health workers[39] in current epidemic has further weakened the available local health human work force. Unfortunately, extreme actions such as 'military lockdown' to comb through the communities to locate hidden patients or suspected patients and forcibly isolating them created further hostility of local population against the public health measures[40]. Some of these

[36] A.S.Fauci, *op.cit.* note 9, p.2.

[37] T.R. Freiden et.al, *op.cit.* note 8, p.2.

[38] Lancet editorial, *op.cit.* note 1, p.637.

[39] WHO, *op.cit.* note 6.

[40] Lisa O'Carroll. 2014. Sierra Leone's planned Ebola lockdown could 'spread disease further'. *The Guardian* 6 September.

challenges can be tackled by coordinated global response of humanitarian and medical aid organizations, as well as through provision of adequate supplies for supportive care, supply of personal protective equipment (PPEs) in required quantities with training on how to use these correctly to avoid infections in health care workers[41]. Other supportive measures to build the trust of local communities in foreign aid organizations and health workers include provision of food for affected populations since isolation of patients takes away their means of sustaining the families[42] and assistance in burial procedures[43]. Given all this complexity, it is no wonder many experts, scientists, media representatives and general populations look at experimental drugs and vaccine candidates as the only hope to successfully curtail the current outbreak. We describe some of the challenges of this strategy in the next section.

We are aware that the need to build public health and disease surveillance infrastructure, community engagement and culturally sensitive communication are uncontroversial strategies that as a general idea do not raise ethical debates. But when it comes to deciding how many resources should actually be channeled towards those structural aspects, there is disagreement. Therefore, we want to highlight the importance of these

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Available at:

http://www.theguardian.com/world/2014/sep/06/sierra-leone-lockdown-ebola-outbreak

[Accessed on 05 Jan 2015].

[41] W.A. Fischer et.al. Protecting Health Care Workers from Ebola: Personal Protective Equipment is Critical but not Enough. *Ann Intern Med* 2014.

[42] T.R. Freiden et.al, *op.cit.* note 10, p.2.

[43] Ibid:2.

aspects for two main reasons. Community engagement and communication will be even more critical when implementing phase II trials for vaccines, repurposed drugs and experimental drugs in affected countries in early 2015. For successful patient recruitment as well as continued monitoring of research participants, it is critical that communities trust research teams and health workers, and essential that they understand trial design, including why (depending on patient randomization or stepped wedge design) some patients or some places will receive experimental interventions and others will not. It is also important to note that even if a few foreign researchers and clinical trial experts are deployed in the field to carry out these trials, most ground work and monitoring of trial participants will be still done by the health workers who are already working in the treatment centers. Being involved in research work and regular follow-up of research participants could impose an additional burden on the health workers who are already responsible for caring and surveillance activities.

A race against time to develop, test and license effective drugs and vaccines against Ebola

Development of a new drug or vaccine is a long process spanning many years to a few decades[44]. Most experimental drugs and vaccine candidates do not cross the 'valley of death' along the spectrum of drug development either because they are ineffective or they are toxic[45]. Apart from being a time consuming process, drug development and testing requires huge

[44] A.Rid & E. Emmanuel, *op. cit.* note 26, p.1.

[45] J. L.Goodman, *op. cit.* note 22, p.2.

monetary resources to bring such experimental drug molecules from the laboratory to preclinical animal studies and eventually to the market after having been thoroughly investigated and tested to assess and ensure various safety, toxicity and efficacy parameters in humans in phase I to III clinical trials. Even though epidemics like this can suddenly mobilize more financial support, political will, international lobbying and support from the regulatory agencies to expedite clinical trials[46] (as is the case with candidate vaccines or repurposed drugs) upscaling production of any new drug molecule under good manufacturing practice (GMP) can take several months if not years[47]. Even when a drug has been produced on a large scale, some such medicines require stringent handling and monitoring while being administered to patients. This often requires intensive care facilities which are mostly lacking in the countries affected by Ebola in Western Africa. On the other hand, drugs and vaccines against infectious diseases like Ebola can only be tested during an epidemic for it will be ethically unacceptable to inject people with highly infectious pathogens such as Ebola to test the efficacy of the drug or vaccine. For the same reasons, the current epidemic of Ebola is an ideal opportunity to test potential therapies and vaccines, provided a study design is used which enables accurate data gathering on the efficacy of experimental interventions in order to guide further clinical drug development, while also maximizing any prospect of benefit and minimizing harm to trial participants/communities.

[46] A. Mullard, *op. cit.* note 21.

[47] A.Rid & E. Emmanuel, *op. cit.* note 26, p.1.

This complex situation requires many different stakeholders including politicians, scientists, clinical trial experts, ethicists and doctors to consider and address various ethical issues related to legal and technical issues such as licensing, production and roll-out, but also ethical issues such as transparency, distributive justice, and respect for autonomy. A collaborative, well-coordinated effort is required to curb the current Ebola epidemic and to make provisions for preparedness towards future epidemics of Ebola or other emerging infectious diseases.

What potential treatment options are being investigated in the current epidemic?

Experimental drugs or're-purposed' drugs

Under an international partnership, two trials are being planned in West Africa, with one led by researchers at Oxford University to test the antiviral drug Brincidofovir which is effective against Ebola in the laboratory but has not been tested in animals yet[48]. The site for this trial has not been finalized yet. The French National Institute of Health and Medical Research (INSERM) will lead another trial in Guinea to test another antiviral drug Favipiravir which has been shown to be effective in animals[49]. Interestingly,

[48] Clinicaltrials.gov. 2014. An Open-Label, Multicenter Study of the Safety and Anti Viral Activity of Brincidofovir (BCV, CMX001) for Ebola Virus Disease. Available at: http://clinicaltrials.gov/ct2/show/NCT02271347?term=Brincidofovir&rank=3. [Accessed on 05 Jan 2015]

[49] Sarah Boseley. 2014. Ebola: experimental drug trials to go ahead in west Africa. Médecins Sans Frontières to start three trials in treatment centres run by volunteers in west Africa. The guardian. 13 November. Available at:

Zmapp is not one of the drugs under consideration to be tested in a clinical trial. This could be due to the time and capacity required to upscale the production of sufficient doses for trials but it is hoped that the sufficient quantities might be available by February or March 2015[50]. Furthermore, drugs already approved for other medical indications could potentially be 'repurposed' for Ebola virus disease (EVD) and tested in humans given the serious nature of the epidemic and absence of any other treatment options[51]. Scaling up the production of any experimental drug under GMP criteria needs time, infrastructure and manufacturing capacity. Even if manufacturing can be scaled up, the next challenge will be to decide who should be prioritized to receive the experimental treatment. The WHO noted clearly that use of experimental or repurposed drugs should not replace standard care and investigation of these interventions must not distract attention from the implementation of standard clinical care, rigorous infection prevention and control, and careful contact tracing and follow-up[52].

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http://www.theguardian.com/world/2014/nov/13/ebola-drug-trials-liberia-guinea [Accessed on 05 Jan 2015].

[50] D. Mohammadi. First trials for Ebola treatments announced.*The Lancet* 2014; 384: 1833.

[51] J. L.Goodman, *op. cit.* note 22, p.2.

[52] World Health Organization (WHO) 2014. Meeting summary of the WHO consultation on potential ebola therapies and vaccines. Geneva, Switzerland. Available at: http://apps.who.int/iris/bitstream/10665/136103/1/WHO_EVD_Meet_EMP_14.1_eng.pdf?ua=1 [Accessed on 05 Jan 2015].

Passive immunotherapy with serum from Ebola survivors

The WHO is also considering using human convalescent plasma, whole blood and other therapies derived from the blood of Ebola survivors as treatment modalities[53]. The current epidemic has about 9000 survivors who could be followed up as potential blood donors. It has also been observed that many communities in Western Africa have low levels of latent infection through ingestion of fruits contaminated with the saliva of infected fruit bats and hence may have protective antibodies in their serum[54]. The prevalence of these antibodies varies from as low as 3% in the coastal population to as high as 34% in some of the communities living close to jungles. This might indicate towards some form of acquired immunity being present in population groups of Western Africa but the antibody titers are not high enough to be used as passive immunotherapy. Another challenge is to test the sero-prevalence of protective antibodies in the West African population as well as in survivors of the current epidemic. This will pose practical, logistic and cultural difficulties due to the meaning attributed to bodily fluids including blood. The Antwerp Institute for Tropical Medicine is leading a trial in Guinea with convalescent serum from survivors as treatment for Ebola patients[55]. Any experimental intervention with blood transfusion must be carefully weighed against the risk of other blood transfusion related infections being transmitted such as HIV, syphilis and

[53] Ibid.

[54] D. G. McNeil Jr. 2014. Many in West Africa May Be Immune to Ebola Virus. The New York Times 5 September. Available at: http://www.nytimes.com/2014/09/06/health/ebola-immunity.html [Accessed on 05 Jan 2015].

[55] D. Mohammadi, *op.cit.* note 50.

Malaria. Screening each blood sample for variety of infections will require robust blood safety infrastructure which is clearly lacking in these countries at the moment. Hasty and almost reactive use of blood transfusion from Ebola survivors to Ebola infected patients as an interim treatment option could do more harm than good given that we do not know whether antibody titers present in the blood of survivors are sufficient to protect infected patients, or indeed how many units of blood or plasma will be required to provide benefit to patients. Before being treated with Zmapp, the American missionary Dr Brently was given a blood transfusion from a 14 year old boy[56], who had recovered from Ebola. His care givers at Grady Hospital in Atlanta stated that his recovery cannot be attributed to this blood transfusion or to administration of Zmapp, and may instead be due to good supportive care and intensive care monitoring[57]. (It is worth noting that more useful surveillance data would probably been provided had Brently received a transfusion or Zmapp, rather than both.)

Candidate vaccines

Two candidate vaccines are being tested in large phase I trials in healthy volunteers in the US, the UK, Switzerland and Mali. The goal of these trials is to assess safety and to attempt to determine an appropriate dose for future phase II efficacy trials. In order for vaccination to succeed as a prevention strategy, it requires adequate time for seroconversion and a certain level of

[56] J. L.Goodman, *op. cit.* note 22, p.2.

[57] Ibid.

saturation in the population to break the transmission of infection via herd immunity.

Trial design

Thus it is clear that we do not have many treatment options that are proven safe and efficacious in humans, which could be produced under GMP on a large scale and could be transported, stored under optimal conditions and administered to the affected populations in Western Africa in the near future to curtail the current epidemic. Even if one of these treatment strategies reaches the stage of being tested in clinical trials, this experimental intervention will have to be treated as a scarce resource and priority criteria will need to be set before undertaking such research in a population affected by Ebola.

Parallel to clinical trials in healthy volunteers it has been recommended that randomized clinical trials should be conducted among the affected population to assess the efficacy of these drugs and vaccines[58]. This is important for two reasons. First, given the sporadic nature of the epidemic, the candidate drugs and vaccines should be tested in settings where naturally occurring infection is present[59]. Second, randomization of the limited supply of experimental drugs enables optimal use of a scarce resource, provided we have well designed clinical trials, meticulous interim trial data analysis and robust data safety monitoring boards[60].

[58] J. L.Goodman, *op. cit.* note 22, p.3.

[59] Ibid

[60] A.Rid & E. Emmanuel, *op. cit.* note 26, p.2.

However, there has been ongoing debate on whether traditional RCT design is ethically acceptable in the context of this epidemic, or whether some other modified trial designs should be used in order to ensure fair distribution of available experimental interventions, while also providing meaningful results and being acceptable to all the stakeholders and communities involved[61] [62] [63] [64]. Transparency and ethical consensus should guide these decisions or we run the risk of further losing the trust of the local communities affected by the disease[65]. While randomization might produce a higher standard of evidence, if the trial design is not sensitive to the needs of the community, recruitment of participants will be challenging. It is likely that adaptive randomized designs will provide acceptable solutions ensuring scientific validity of results while also meeting the needs of the community.

Who are the health care workers?

Many countries in West Africa have health systems which need major strengthening. Apart from a lack of physical infrastructure, diagnostic and therapeutic facilities, supply of drugs, and other materials required for

[61] S.Joff. Evaluating novel therapies during the Ebola epidemic. *JAMA* 2014; 312(13):1299-1300. doi:10.1001/jama.2014.12867.

[62] C. Adebamowo, O. Bah-Sow, F. Binka, et al. Randomised controlled trials for Ebola: practical and ethical issues. *The Lancet* 2014 ; 384(9952): 1423-1424.

[63] J. Cohen & K. Kupferschmidt. Ebola vaccine trial raises ethical issues. *Science* 2014; 346(6207): 289-290.

[64] D. Shaw. Randomization is essential in Ebola drug trials. *The Lancet* 2014

[65] A. Saxena. Ebola virus disease outbreak: incorporating ethical analysis into the health system response. Indian Journal of Medical Ethics 2014; xi.

infection control, they also have extremely limited health care work force as is evident from physician to patient ratio of 86,000 patients per physician in Liberia and 45000 patients per physician in Sierra Leone[66]. As we have already highlighted, this epidemic has taken a major toll on health care workers, with an average case fatality of 57% as compared to an average case fatality of 39% in the general population.

A health care worker is any person involved in the provision of care for patients infected with Ebola in formal health care settings. There are also non-medical care givers in home settings, such as immediate family members; unfortunately, the question of whether they should be included in the group of "health care personnel" when it comes to defining priority access to experimental interventions is beyond the scope of this paper. By health care workers we mean everybody in a health center or a treatment facility providing care and treatment for patients suspected or diagnosed with Ebola from admission to the center till the burial in case of death. These include doctors, nurses, laboratory staff, cleaning staff, and other support staff in centers such as laundry workers, ward assistants, security guards, those handling hospital waste, those handling the bodies of dead patients in the hospital, and those involved in assisting the families in burial. There is also another cadre of health workers who are mostly volunteers: young men and women who work as community outreach staff. These volunteers speak the local languages and assist foreign aid workers and hospital surveillance teams to go into communities to identify and isolate suspected cases and follow up contacts. These workers play a crucial role in

[66] C. del Rio et.al, *op. cit.* note 5, p.1.

community based surveillance and form the bridge between the community and health care services. Though the risk profile of each of these categories of people involved in health care provision varies slightly, they all form a team of people who are at the forefront of fighting Ebola outbreak. We also want to highlight that these might include a few foreign professionals and experts but a large proportion of these are local health care workers and rather than differentiating them as foreign or local, we want to consider them as a group of health care workers who need to be protected.

Why should health care workers be prioritized?

Our main thesis is that the health care workers who are at the forefront of treating Ebola patients in the countries affected by this epidemic are at greatest risk and should therefore be given priority for the administration of experimental drug or candidate vaccines during phase I/II trials, and should also receive priority treatment once clinical trials have established the efficacy and safety of these interventions. In addition to their being at higher risk, treating them can in turn confer the greatest benefit to others, and they are more likely to understand the risks of participation in early expedited clinical trials and its modified study design. In the following text, we set out the reasons underlying these three main arguments.

Health workers working in local health facilities run the highest risk of being infected with Ebola due to their exposure to patients in various stages of disease progression and to lack of adequate infection control measures. Though effective, the barrier method of infection control is not always possible in the field because of inadequate supply of PPE, rubber

gloves, other barrier clothing and aprons and supplies for infection control[67]. It has been noted that physical exhaustion, mental fatigue, emotional strain and working in hot conditions while wearing PPE are a few reasons that make health care workers more likely to get contaminated particularly while taking off PPE at the end of their work shift in treatment centers[68]. Local Ebola experts such as Dr Khan in Sierra Leone died during the epidemic, further weakening local expertise[69]. Many health care workers have seen their colleagues become infected and die through weeks and months of this epidemic and that has taken emotional toll on them resulting in many who decided to leave their jobs. But there remain others, such as one nurse who is still continuing to fulfil her responsibility even after witnessing the death of 15 of her nursing staff[70]. Apart from provision of necessary protective equipment and supplies for supportive care, it is important that these healthcare workers themselves feel safe and cared for. The assurance that the global community is taking solid steps to provide them with safety and protection will boost their morale.

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[67] W. A. Fischer, *op.cit.* note 41.

[68] Ibid.

[69] A. Pollock. 2014. Opting Against Ebola Drug for Ill African Doctor. *The New York Times* 12 August. Available at: http://www.nytimes.com/2014/08/13/world/africa/ebola.html?_r=0 [Accessed on 05 Jan 2015].

[70] A. Nossiter. 2014. Those Who Serve Ebola Victims Soldier On. The New York Times 23 Aug. Available at: http://www.nytimes.com/2014/08/24/world/africa/sierra-leone-if-they-survive-in-ebola-ward-they-work-on.html [Accessed on 05 Jan 2015].

We believe that both local and foreign health care workers in the field should get priority access to experimental interventions if they become infected and to any experimental vaccines as part of the proposed clinical trials. This conclusion is based on the following reasoning: First, their continuing actions towards patient care despite major risk to their own lives should be valued and reciprocated. The assurance that they will be cared for in whatever way possible, either by vaccination or experimental interventions, will boost their morale and dedication to their work, and could prevent further loss of health workers due to fear of getting infected.

Second, the need for nondiscrimination within the health care work force while considering access to experimental interventions should also be highlighted. Along with local health care workers, there are some foreign health care workers working in Ebola-affected countries as part of various international health care organizations and faith based organizations. MSF has been vocal on the need for support to carry out their work in these countries[71]. International organizations often airlift their staff in disaster, emergency and epidemic situations for the sake of their safety. This was what happened to two American health workers who were treated with Zmapp and airlifted to the US. These decisions are made by the international organizations and the nations whose citizens are stationed in these field assignments often have strong political and financial commitment to protect their citizens. But the local health care workers and their governments who are struggling to combat the epidemic do not have such means to ensure the safety of their staff at their disposal. This is

[71] Lancet editorial, *op.cit.* note 1, p.637.

evident in the fact that the local health work force has sustained the major impact of this epidemic in terms of both infection rate and mortality rate[72]. Discrimination against health care workers based on their employer or nationality can only demotivate local health care staff leading to loss of health work force due to frustration or fear and will further negatively affect the local health system. While foreign and local health workers have equal basic moral claim on access to experimental drugs, a further argument could be made based on the fact that foreign workers are likely to benefit from a superior standard of care in their own countries. This might be used to claim that local workers who do not enjoy such advantages should be prioritized to receive experimental interventions. It should be noted that not all foreign health workers come from the US, the UK or other developed countries, and it should not be assumed that they will always have access to better care and treatment facility in their home countries[73]. Therefore, rather than arguing in favor of foreign or local health workers, we recommend prioritization of all health care workers for inclusion in clinical trials of experimental interventions. Furthermore, some foreign workers may choose to be airlifted to their home country instead of taking the risk of being included in a trial of an experimental intervention and are obviously free to do so as long as their employers or charity organizations bear the cost of

[72] WHO, *op.cit.* note 6.

[73] D Trotta. 2014. Cuban doctor in Sierra Leone tests positive for Ebola. *Reuters* 19 Nov. Available at: http://www.reuters.com/article/2014/11/19/us-health-ebola-cuba-idUSKCN0J308820141119. [Accessed on 05 Jan 2015].

their evacuation and treatment. If many foreign workers choose this option it will allow more local workers to be included in trials.

Third, non-discriminatory access for local and foreign health care workers is warranted because both play important roles. We should remember that foreign health care workers cannot perform their medical duties without support and insight from locals. Local health workers not only provide medical care, but are also the link between the foreign health workers and local communities; they speak the local language, understand local customs and beliefs and often act as intercultural communicators. This is a valuable resource in itself and their vast experience of the local field reality will be critical to maintain the trust of local communities, to work with these communities to control the epidemic. This can be very well seen in terms of communities' attempts to hide sick family members or individuals. Local health workers are much more likely to understand local community beliefs in addition to western biomedical and epidemiological principles of epidemic control. Without this expertise, it will be virtually impossible to put an end to this epidemic and hence this work force deserves protection and support.

In addition, local health care workers are likely to return to work faster than the foreign health workers and will continue to work in the field even when the epidemic has ended and foreign experts have left the field. Furthermore, the local health care workers who survive this epidemic will be an invaluable and experienced resource in future epidemics in these countries as well as in neighboring countries in Africa. However, we are also aware of the fact that without assistance of foreign health workers and Ebola experts, the local health work force alone cannot combat this

epidemic. Rather than prioritizing one group over the other, we argue that both local and foreign health care workers should be treated as valuable resource and provided adequate protection, opportunity and access to experimental interventions.

Use of experimental interventions (in a randomized controlled trial, or modified RCT design) that have only been tested on animals or have limited human data also requires good understanding of the risks involved on the part of research participants. The severity of the current epidemic and the resulting loss of human life are likely to influence the ability of the general population infected and affected by the epidemic to fully understand the experimental nature of the intervention and the risk involved including serious adverse reactions and deaths. If an experimental intervention is used on a large scale in population and many ill patients die, this could have a serious backlash on whole effort to provide possible care and to control the epidemic (whatever the reason for the deaths; lack of efficiency of the drug, severe adverse reactions or simply because the disease had progressed too far before the treatment could be given). The widespread belief that poor patient populations in developing countries have been used unethically in clinical trials by Western pharmaceutical companies could be further reinforced, and communities might further lose their trust in Western medicine. Against this backdrop, health care workers are in a better position to understand the nuances of use of experimental interventions for the first time in humans in a public health emergency such as this epidemic. Their knowledge of medicine, disease pathology, clinical trials and risks makes it more plausible to obtain valid 'informed consent' from them, whether in a trial or in clinical care. This third argument applies equally to foreign and

local healthcare workers. We are not stating that it is impossible for the general population to understand the risk of such experimental interventions, hence making it impossible to obtain their true informed consent. Rather, given the impact of this epidemic on communities and families who have lost their loved ones and have very limited financial resources, the conditions under which they decide to participate in clinical trials are far from ideal. In contrast, healthcare workers have additional expertise that makes it more likely that they will be able to provide informed consent.

Potential constraints and challenges

We are well aware that our arguments to prioritize the health care work force for access to experimental interventions in case of infection may be criticized for a few reasons. One ethical concern will be the fact that one profession gets priority over all other suffering people and this could be seen as an utilitarian approach. However, the point can be made in response that saving healthcare workers will ultimately allow more members of public to be saved. We do not claim that health care workers are more important than the general population, but we cannot protect and care for the general population without adequate and healthy health work force, and it is in the interests of ordinary citizens to prioritize healthcare workers for treatment.

A second practical concern relates to the financial resources required to get access to the experimental drugs. We will need an international response including financial commitment to break the transmission cycle of Ebola for the simple fact that the epidemics such as these do not remain as

burden of only the affected countries but rather have global impact and hence need a global action and commitment[74].

A third challenge will be to use the resources in an ethical manner whether it is in terms of financial aid or supply of vaccine or drug in donation. Having pre-set and agreed upon criteria for fair and transparent distribution of drug doesn't mean it will be implemented in the same manner. Local corruption, power dynamics and hierarchies among the health care professionals as well as between the rich and the poor of the country, it will take well-coordinated and well-monitored system to ensure optimal and just distribution of resources.

Conclusion

The transmission of Ebola cannot be combated without supporting and strengthening human resources in healthcare in West-Africa. Healthcare workers should be prioritized for enrolment in clinical trials with experimental drugs or vaccines because they are at greatest risk, treating them can confer greatest benefit to others, and they are more likely to understand the risks of participating in such trials of experimental interventions with limited or no prior data of safety and efficacy in humans.

[74] Lancet editorial, *op.cit.* note 1, p.637; T.R. Freiden et.al, *op.cit.* note 10, p.2 ; A.S.Fauci, *op.cit.* note 11, p.3.

Chapter 8

Not Fit for Purpose: The Ethical Guidelines of the Indian Council of Medical Research

Priya Satalkar, David M. Shaw

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Abstract

In 2006, the Indian Council of Medical Research (ICMR) published its 'Ethical guidelines for Biomedical Research on human participants'. The intention was to translate international ethical standards into locally and culturally appropriate norms and values to help biomedical researchers in India to conduct ethical research and thereby safeguard the interest of human subjects. Unfortunately, it is apparent that the guideline is not fit for purpose. In addition to problems with the structure and clarity of the guidelines, there are several serious omissions and contradictions in the recommendations. In this paper, we take a close look at the two key chapters and highlight some of the striking flaws in this important document. We conclude that ethics committees and national authorities should not lose sight of international ethical standards while incorporating local reality and cultural and social values, as focusing too much on the local context could compromise the safety of human subjects in biomedical research, particularly in India.

Keywords

Bioethics, clinical trials, guidelines, India, patient protection, research ethics

Introduction

In recent years, India has developed as a key hub for conducting clinical trials. This has been attributed to various factors, including: the interesting disease profile of its population; the rising prevalence of chronic and life style diseases, along with a high burden of infectious diseases like tuberculosis, HIV, and malaria; a vast treatment-naïve population; the manpower and infrastructure to conduct clinical trials at significantly lower cost; and weak government policies and regulations. All of these factors attract large number of international pharmaceutical companies to conduct trials here.[1] This has also led to a number of controversies and protests by the local NGOs and health activists.[2] The Government and particularly the Supreme Court of India have taken a strong stand against international pharmaceutical companies in recent months, as was evident in a lawsuit against Novartis, whose plea for extension of patent for Glivac was rejected by the Supreme Court. [3][4][5] Furthermore, the deaths of young girls in HPV vaccine trials has created another ethical debate concerning whether these trials should have been allowed to take place[6] and whether procedures were meticulously followed to ensure safety of human subjects.[7] Recently, in a statement issued by the Ministry of Health and Family Welfare, the Health

[1] *K.L.Bairy & P.Pereira. Accreditation of human research protection program: An Indian perspective. Perspect Clin Res2012; 3: 80-84.*

[2] PTI. 2013. Protest against Novartis' attempt to obtain patent for Glivec in India.*The Hindu Businessline 24th Feb:*

[3] EP News Bureau. 2013. New rules on compensation to make clinical trials in India 'virtually impossible': ISCR. *The Express Pharma.* 7th Feb:

[4] *K. Jayraman. Gleevec loses Indian patent battle. Nat Biotechnol 2013; 31:371.*

[5] K. Kulkarni & S. Mohanty. 2013. Novartis loses landmark India patent case on Glivec. *Reuters* 2nd Apr:

[6] P. Shetty. 2012. Indian HPV Vaccine Trial should never have happened. *Nature Newsblog* 21June:

[7] Alliance for Human Research Protection (AHRP). 2011. Report Blasts Unethical HPV Vaccine Trial in India. New York, NY: AHRP. Available at: http://www.ahrp.org/cms/content/view/805/52/ [Accessed 24th May 2013].

Secretary stated that in the last seven years 57303 human subjects were enrolled in clinical trials of 475 new drugs, 39022 subjects completed trials, and 11972 serious adverse events (excluding deaths) were reported; 2644 deaths were reported out of which 80 could be attributed to trial drugs.[8] These numbers may be only the tip of iceberg. The ethical issues underlying clinical research in India are very complex and have only rarely been discussed in the literature. Therefore, we decided to review the ethical guidelines issued by the relevant Indian authorities to attempt to increase our understanding of the situation; what we found was troubling.

The third version of the 'Ethical guidelines for Biomedical Research on Human Participants' was published by the Indian Council of Medical Research (ICMR) in 2006.[9] Although no clear reasons were provided for developing this guideline, the introduction states that it accounts for 'unique challenges faced in India to translate universal ethical principles to biomedical research in multicultural Indian society with multiplicity of health care systems of considerably varying standards'. The introduction also states that universal ethical standards should not be violated while conducting biomedical research in India and that researchers need to consider local cultural values while applying the universal ethical principles of autonomy and informed consent.

While this intention to translate universal ethical values and principles into local culturally and socially sensitive values is admirable, there may be a danger of becoming too local and hence compromising

[8] D. Mahapatra. 2013. 2,644 died during clinical trial of drugs in 7 years: Govt to SC. *The Times of India*. 25th Apr.

[9] Indian Council of Medical Research (ICMR). 2006. Ethical Guidelines for Biomedical Research on Human Participants. New Delhi, India: ICMR. Available at: icmr.nic.in/ethical_guidelines.pdf [Accessed 24 May 2013].

universal ethical standards. Careful study of the document raises doubts about whether it succeeds in providing clear 'guidelines', both in terms of applying universal ethical standards and translating these into the local context.

In this paper, we critically analyze two chapters of the ICMR guidelines and argue that the text lacks clarity and consistency, is written in a complex language with long convoluted sentences which can be interpreted in number of ways, is vague about ethical issues and standards and does not provide concrete 'guidance' for biomedical researchers. We highlight a few general and specific problems in these two chapters and argue why these could be problematic; they leave a number of loopholes in the guideline that would allow researchers to escape responsibility for unethical research. Finally, we provide suggestions for improving the document.

OVERALL STRUCTURE OF THE ICMR GUIDELINES

This 111 page document can be found on the ICMR website in the publications section under the subheading Ethics (http://icmr.nic.in/ethical_guidelines.pdf). The document is divided into two main parts: The first provides a Statement of General Principles on Research using Human Participants in Biomedical Research, and the second revolves around Specific Principles on Research using Human Participants in particular areas of biomedical research such as clinical evaluation of drugs/devices/diagnostics,/vaccines/herbal remedies/Ayurvedic, Siddha and Unani medicine, epidemiological studies, human genetics and genomics

research, research in transplantation and assisted reproductive technology. For the purposes of this paper, we focus on the first two chapters of this guideline, which are the Statement of General Principles and the ethical review procedure. For each of these chapters, we will first describe general issues and then address more specific problems.

STATEMENT OF GENERAL PRINCIPLES ON ETHICAL CONSIDERATIONS INVOLVING HUMAN PARTICIPANTS.

General issues

This chapter is written in a very unusual style that was difficult to understand. Twelve ethical principles are provided, ranging from ‘essentiality’ to ‘totality of responsibility’ (see Box). It is interesting to note that many of these principles are never used in the international literature. This document does not elaborate on the source of or the reasons for choosing these twelve principles. It could be seen as an effort to accommodate the local and cultural needs specific to the Indian context by expanding these principles. However, it remains unclear whether this long list actually adds anything new that is not covered by existing international guidelines or indeed whether it actually protects research participants in India. Furthermore, the language used to describe the principles is ambiguous. Even if we keep in mind the fact that this chapter only highlights the ethical principles, the use of sentences as long as a full paragraph leave the reader somewhat confused, even after close reading. If this is the situation for readers trained in ethics, a lay person would probably

encounter even more difficulty. As an example, here is the first general principle:

> **Principles of essentiality** whereby the research entailing the use of human participants is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well-being of the planet.

General Ethical Principles:

1. Principles of essentiality
2. Principles of voluntariness, informed consent and community agreement
3. Principles of non-exploitation
4. Principles of privacy and confidentiality
5. Principles of precaution and risk minimization
6. Principles of professional competence
7. Principles of accountability and transparency
8. Principles of the maximization of public interest and of distributive justice
9. Principles of institutional arrangements
10. Principles of public domain
11. Principles of totality of responsibility
12. Principles of compliance

Research guidelines are often written for diverse audiences including doctors, nurses and trial coordinators; they aim to provide guidance in a technically correct, simple and clear format. This chapter obviously falls short in terms of both these objectives. Another problem with this writing

style is that one could interpret the same statement differently based on interpretation of grammar, leaving great scope for selective interpretation of principles. It is unclear why the opening and arguably most important chapter of this guideline was written in this way, given that there is a high risk that people might give up reading the guideline further, even though the rest is written in much simpler format. In short, this chapter discusses almost everything from the wellbeing of the planet to the *mutatis mutandis* nature of informed consent, but leaves everything extremely vague, unclear and prone to misinterpretation. A cynic might suggest that the guideline is deliberately vague so almost any biomedical research involving human participants being planned in India could get ethical clearance, thus safeguarding the interest of the research and industry lobby.

Specific issues

Although we could critically comment on each of these 12 principles, we will instead focus on and highlight only three of these principles and demonstrate how they can be misinterpreted or selectively interpreted. It must be noted that there is no specific mention of the individual importance of each of these 12 principles, so it is unclear whether they are of equal importance or are arranged in order of importance, or which principle should prevail if there is a conflict between two principles, and what process should guide this.

Principles of voluntariness, informed consent and community agreement

This is the most elaborated principle of the twelve and has a few clear strengths in terms of addressing the information given to the participants, their right to withdraw, competence and the voluntariness of consent procedure. But it raises an interesting question about treating the community as a research participant:

> '….Where any such research entails treating any community or group of persons as a research participant, these principles of voluntariness and informed consent shall apply, *mutatis mutandis*, to the community as a whole and to each individual member who is the participant of the research or experiment…'

The first problem with this passage is that many readers will not understand the meaning of this Latin phrase. The second is that it is unclear what it would mean to treat an entire community as a research participant. The third is that "mutatis mutandis" means that only aspects that need to be changed should be changed, which does not provide any meaningful guidance whatsoever. As such, this sentence is almost entirely useless.

However, towards the end of this paragraph, the guidelines state that 'the nature and form of the informed consent and the evidentiary requirement to prove that such consent was taken shall depend on degree and invasiveness of research….Ethics committees shall decide on the form of consent to be taken or its waiver based on the degree of risk that may be involved.' This raises a number of issues such as how risk should be evaluated by Institutional Ethics Committees or Institutional Review Boards (IECs/IRBs) while conducting ethical review of research projects, which is

in the focus of the second chapter of this guideline. This section of the guidelines is perhaps attempting to translate the international ethical standard for informed consent to the local and cultural needs of India. However, doing so undermines the rights of the research participant by stating that the IECs will decide and instruct the researchers on the nature and form of informed consent to be obtained and of the evidentiary support that such consent was obtained. In HPV vaccine trials, those in charge of the hostels where these young girls were living gave "informed" consent on behalf of the girls;[10][11] this was considered adequate despite clearly falling short of international standards. Parents of the girls were not even aware that the girls were part of research and were given a trial vaccine. Perhaps the IECs thought that vaccination as part of a phase IV trial was not a substantial risk and that it was therefore sufficient to obtain blanket consent from the hostel warden rather than contacting the parents of the girls, who might be illiterate and hence unable to understand the nature of the research. Alternatively, they may have thought that approaching parents for consent for the HPV vaccine could be culturally inappropriate and problematic since it implies sexual activity among adolescent girls (and women) which is a taboo subject in India, meaning that the parents would be reluctant to give such consent. If this is the translation of international ethical standards as per the local cultural norms, it feels more like an interpretation of convenience rather than a need- based local translation. Thus, the current guideline actually supports what was done in the HPV vaccine trial if

[10] Aarti Dhar. 2012. Government warns PATH. *The Hindu 25 August*:
[11] SAMA: resource Group for Women and Health. 2010. Trial and Error: Ethical Violations of HPV Vaccination Trials in India. New Delhi, India. Available at: http://samawomenshealth.wordpress.com/2010/05/17/trial-and-error-ethical-violations-of-hpv-vaccination-trials-in-india/ [Accessed 24May 2013].

looked at from this perspective. But the question remains: should this be the intention of a national guideline designed to protect research participants?

Principles of accountability and transparency

This principle dictates that research is conducted in a fair, honest, impartial and transparent manner. It mandates all those involved in the research to fully disclose each aspect of their interest in particular research, including any conflict of interest. This makes perfect sense. However, the principle further states that '…., subject to principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research … should be retained for a reasonable period…' The principle of privacy and confidentiality is elaborated as principle number IV but there is no explicit mention of the rights of the researcher anywhere in this chapter; nor is there any reference to it. It is unclear both what these researcher rights are, and how are they linked to preserving all the research data and notes for a predefined period of time and making this data available for scrutiny by other researchers or the appropriate legal or regulatory bodies. The phrasing of the sentence, with 'subject to' could also be read as implying that the principle of privacy and confidentiality and the rights of the researcher prevail over the requirement to preserve the research notes and making them available for scrutiny by appropriate bodies; as such, this principle could in fact facilitate research misconduct by allowing it to remain hidden.

Principles of totality of responsibility.

This interesting principle is stated as one single long statement broken down with numerous commas and clauses. Fundamentally, it states that the responsibility of ethical conduct of particular research falls on everyone involved directly or indirectly with the research:

> **Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

It is commendable that this statement of responsibility is so inclusive, but what does this all really mean? If everyone is responsible, it is easy to pass the buck from one responsible member to the other till one finds the weakest scapegoat who can be blamed when something goes wrong. In a country like India, when everyone is responsible, this often translates in reality as no one is really responsible for anything, because everyone thinks that somebody else is responsible. The suggestion that those who use or

derive benefit from the research are also responsible is also problematic. It seems bizarre to argue that patients or research participants who benefit from having access to care and treatment by just being part of the research[12], are also responsible for ethical conduct of the research.

The issue of who is responsible for the ethical conduct of research becomes a particularly interesting question when something goes wrong with the research or with the research participants, resulting in serious adverse events or death. In many previous cases in India, the ball of responsibility for research/trial related deaths is often passed from one stakeholder to the other and eventually to research participants, and matters are covered up. This was the case with the lack of ethical standards around informed consent and deaths in HPV vaccine trials. According to this guideline everyone is slightly responsible and thus no one is truly responsible.

ETHICAL REVIEW

General issues

Responsibilities of Institutional Ethics Committees (IECs)

The document defines the responsibilities of IECs as follows:

- Conducting competent and objective review of ethical aspects of submitted research proposals
- Conducting scientific review of submitted research proposals in case there is no separate body to carry out such scientific assessment.

[12] J. Y. Shah &et al. What Leads Indians to Participate in Clinical Trials? A Meta-Analysis of Qualitative Studies. *PLoS one 2010 ; 5 : e10730.*

- Advising researchers on safety and well-being of research participants
- Protecting dignity, rights and well-being of research participants
- Ensuring that universal ethical values and international scientific standards are expressed in terms of local community values and customs
- Assisting in the development and education of research community responsive to local health care requirement.

It is good to clarify various responsibilities of IECs beyond the ethical review process such as their advisory role and role in capacity building for the local research workforce, but no further details are provided how this can be achieved in practice. Two of the responsibilities above need further discussion. The first is the segregation of the scientific and ethical aspects of the research proposal being reviewed. It is not clear that the scientific and ethical aspects of any given research proposal can be separated in this way; scientifically weak research is itself unethical.[13] The other aspect concerns expressing international scientific standards and universal ethical principles in local values and customs. We believe that this responsibility should not be put on IECs, which are often local and affiliated with research institute and public hospitals attached to medical schools. In a country as large and diverse as India, this might lead to varied and multiple translations of 'universal' into 'local' thus losing the essence of universal ethical standards. It would be more appropriate to carry out this task at national or at least

[13] *David Shaw & Bernice Elger. The relevance of relevance in research. Swiss Med Wkly2013; 143: w13792.*

regional level so that such translation of ‘universal’ to ‘local’ ethical standards and values is carefully discussed.

Constitution of IEC/IRB

The guideline states that IECs/IRBs should be multidisciplinary and multisectorial and have independence and competence as their core values. It is recommended that the chairman of such committee should be from outside the institution to maintain the independence of the committee, but that the secretary who is responsible for the day-to-day organization and function of the IEC should be from the same institution. Though an IEC should include experts, patient representatives and lay people, a large responsibility is put on the secretary. It is the secretary who assesses the level of risk involved in each submitted research proposal, which is the basis for deciding whether the proposal is eligible for exemption from review, or requires expedited review or complete review (see below). During the review process, it is also suggested that the secretary and the chair can review the proposals for expedited review and pass the summary of this review to other IEC/IRB members. Given that the secretary is expected to review proposals, this cannot be a mere secretarial position; a member of the administrative staff would lack the necessary training to scientifically or ethically review proposals. Even if the secretary is medically or scientifically qualified, one must keep in mind the particular hierarchical work culture in India and the power relationships between secretaries and their superiors. In this context, it is questionable whether a secretary can really speak up for him or herself especially if his/her views

are clearly not in line with those shared by the chairman of the committee. The role of the secretary also raises questions about the independence of the review process. In their current state, the guidelines suggest that a secretary could themselves review all the proposals sent to a committee by identifying them as minimal risk even if they were potentially very harmful; given that the secretary can be a staff member at the institution that wishes to conduct the research, this is ethically problematic.

Training of IEC members

The guidelines state that IEC members should keep themselves updated on all national and international developments in ethics by undergoing regular training. However, it is not stated who should organize, certify, or monitor the quality and content of these training programs, and how many hours per year each committee member should spend on training. The guidelines further state that for drug trial review, it is preferable to train IEC members in Good Clinical Practice, but it is not stated which GCP document is being referred to, given that India has its own document called Indian Good Clinical Practice.[14] One could also ask whether being trained in ICH-GCP is enough for the IEC members to be able to conduct ethical review of drug trials competently, given the inherent weaknesses of that document.[15] Furthermore, the only mention in the ICMR guidelines of the Declaration of Helsinki, which is one of the key international documents on ethics and human subject safety, is in the form of its note on clarification on paragraph

[14] Central Drugs Standard Control Organisation (CDSCO). 2001. Good Clinical Practices For Clinical Research in India. New Delhi, India. Available at: http://cdsco.nic.in/html/GCP.htm [Accessed 24 May 2013].

[15] *David Shaw & Alex Mcmahon. Ethicovigilance in Clinical Trials. Bioethics 2012. doi: 10.1111/j.1467-8519.2012.01967.x*

30, which was added by the WMA General Assembly in Tokyo in 2004. The omission of any mention of the importance of this key international standard for the protection of research participants is troubling.

Monitoring, regulation and accreditation of IRBs and IEC (Ind)

The ICMR guidelines suggest that in cases where there is no appropriately constituted IEC, the researchers can submit their research proposals to an independent IEC (Ind). It is not clear how IEC (Ind)s are created, function or are monitored. In India, anything that is independent and hence outside the realm of regulatory mechanisms and monitoring often features many irregularities. Private medical practice in India is a good example of this. Even internationally, the quality of ethical review process by independent or private IRBs and IECs has been debated.[16] It is often argued that private or independent ethics committees, by their very structure and organization, could have innate conflicts of interest which could diminish their neutrality and objectivity in the ethical evaluation of submitted research proposals. Given this context, there needs to be detailed discussion on the need for private or independent IECs. If IEC (Ind) are perceived to be a necessity for those researchers who do not work at Institutions with their own IECs, close attention must be paid to how these IEC (Ind)s can be regulated or monitored. Recent controversy about trials conducted with 'mentally challenged' individuals in Indore, India from 2008 to 2010 has highlighted the problematic role of commercial/independent IECs in ethical review and

[16] *T. Lemmens & B. Freedman. Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards. Milbank Quarterly 2000;78: 547-584.*

approval.[17] Mechanisms need to be put in place to ensure that these entities can conduct competent ethical and scientific review of submitted proposals. Otherwise, there is a danger that the clinical trial organizations might start conducting their research and trials in the vast rural areas of the country which have no IECs but do have large treatment-naive populations to recruit in their research and hence start submitting their applications to IEC (Ind).

The same questions can be asked about the quality and work of appropriately constituted IECs which are affiliated with large institutions and teaching medical hospitals.[18] What quality control measures are in place to ensure that these IECs have competent and well-trained staff and the review process conducted by them is rigorous and well documented at every stage of the research? The document suggests that an authority will be set up under the proposed bill on 'biomedical research on human participants' that will require all IECs to register themselves with this authority. This authority will be responsible for monitoring functioning of IECs and developing mechanisms for enforcing accountability and transparency by these IECs. The creation of such an entity needs to be thought through adequately, and mechanisms need to be in place to ensure accountability and transparency of this authority itself.

[17] *A. Bhan. Clinical trial ethics in India: One step forward, two steps back. J Pharmacol Pharmacother 2012; 3(2): 95–97.*

[18] *R. Kadam & S. Karandikar. Ethics Committees in India: Facing the challenges! Perspect Clin Res. 2012; 3: 50-56.*

Specific issues concerning review procedure

Definition of minimal risk and categorization of research proposals

Minimal risk is defined as 'one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of general population or during the performance of routine physical and psychological examination or tests'(p.11). It is further states that '… in some cases like surgery, chemotherapy or radiation therapy, great risks would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current everyday life' (p.11). No references are provided for this particular way of understanding minimal risk, which is somewhat idiosyncratic. It is true that radio- and chemotherapy pose great risk to patients, but to subject research participants to *additional* radiation or drugs on top of their therapy certainly does not constitute minimal risk. If the guideline means simply that including such patients in a trial with minimal intervention constitutes minimal risk, then it is stating the obvious. If minimum risk is defined in relation to risk in everyday life events, is it justified to subject Indian research subjects to higher levels risk than would be acceptable in the developed world simply because the risk of everyday life events in India is higher than in other countries?

Minimal risk actually forms the starting point for all the research proposals to be categorized into the distinct categories of exempted from review, expedited review and complete review. It is unclear how this happens in practice, given the vague definition of minimal risk. The

guideline defines three different categories of review and each of these categories is problematic in itself. Here, we provide few contradictory statements related to these categories and the review process. In the preamble to ‘full review’ on page 14, the document states that various situations and risks involved in research proposals should be evaluated in terms of the existing facilities at a given research site. This means that depending on a research site, the same research proposal could be seen to present minimal risk at a ‘good’ site but more than minimal risk at other research sites. Would it thus attract expedited or exempted review in one site but full review at the other? The guidelines do not address this point, and such a system would be highly unusual.

On page 12 the guideline states that the secretary and chair of the IEC or a designated member of a subcommittee can conduct an expedited review of all proposals which present no more than minimal risk and then lists various such situations including research in emergency situation and research on disaster management. On page 14, it is stated that all research presenting with more than minimal risk and proposals which do not qualify for exempted or expedited review shall be subjected to full review by all the members. But on page 18, under the heading of review process, it is claimed that it should be stated in a committee’s SOP whether the review should be done by all members or the primary reviewer(s), in which case a brief summary of the project, with informed consent and patient information sheet, advertisements or brochures if any should be circulated to all the other members. It is not clear who are the primary reviewers and how are they selected. How can there be a primary reviewer if all the research

proposals should be reviewed by all the members of the IEC? To be fair, this could be simply due to bad structure of the document but that seems highly unlikely. If we try to reconcile these statements, we could conclude that the proposals with no more than minimal risk which are categorized for expedited review actually undergo more rigorous review than "riskier" proposals subjected to the general review process.

In the category of expedited review, sub point five states that in emergency situation like disease outbreaks or disaster, full review may not be possible. In these situations, an expedited review might be acceptable for pilot study or preliminary study to understand the safety and efficacy of the intervention. But then it further states that the same participants should not be included in the clinical trial that may be initiated later based on the findings of this pilot study (p12). It is not clear how it can be ethically justified that the same participants should not be included in later trials especially if the intervention is believed to be useful.

The section on expedited review also refers to research on interventions in emergency situations. According to section 2.5.a., in certain emergency situations where no standard therapy exists, a physician might try an investigational drug/device/vaccine on patients as an intervention when consent of person/patient/responsible relative or custodian/team of designated doctors for such an event is not possible (p13, i). It is extremely questionable whether a "team of designated doctors" could give meaningful informed consent for an emergency intervention, whether for research or just for medical care and treatment. Further on, at point IV, the document states that such an emergency intervention is acceptable if a data safety

monitoring board is constituted to review the data. This confuses matters further because it appears that this is related to emergency intervention research; if it is ongoing research, why should such emergency intervention research not be treated like any other research proposal and require complete review, rather than receiving expedited review?

Process of ethical review and decision making

The document provides details of how research proposals should be submitted for ethical review and urges IECs to continue the review process after initial approval of the study through periodic, continuing and interim review. But the actual review process itself is hardly explained at all, and this small section is towards the end of this chapter. It suggests that the method for review should be stated in the standard operating procedure (SOP), but it is not clear who is responsible for developing these SOPs. This might be interpreted as meaning that each IEC can develop its own SOP. The SOP would also determine whether the review should be conducted by all reviewers or by primary reviewers. The guideline states that the decision on approval of submitted research proposal should be made by broad consensus but does not state how various aspects should be discussed and how various conflicting ethical principles should be balanced before reaching a broad consensus.

CONCLUSION

ICMR set out to develop this guideline with the noble intention of translating international ethical principles and scientific standards into

locally sensitive and culturally appropriate values to guide all the research on human subjects taking place in India. Their effort to have a large number of experts and various committees working together on this document, has led to number of different voices and writing styles in this document which often seems highly influenced by legal language, especially in the first chapter. The guideline has multiple inconsistencies and ambiguities that may sometimes be attributable to writing style but sometimes appear to be intentional and confuse the reader. The vagueness of the guidelines could be interpreted as being intended to facilitate research rather than to protect participants. At a minimum, the guideline needs to be revised to remove these inconsistencies and clarify some of the issues pointed out in this paper. We would go further and recommend that an entirely new guideline be written 'from the ground up' as an urgent priority in order to protect the tens of thousands of people who enroll in clinical trials every year in India.

Chapter 9

Discussion

Priya Satalkar

Outline

The aim of this research project was to explore and discuss challenges in the translational research of medical applications of nanotechnology with a particular focus on first-in-human (FIH) trials. This chapter describes various insights obtained from this research project in light of existing socio-political debate. The ecological model theory is used to explain the current practice of translational research in nanomedicine and interactions among the key stakeholders. An analysis of issues related to ethical and drug regulatory review of investigational nanomedicine products indicates that new and special regulation for nanomedicine and nanotechnology is not necessary. Rather, the focus should be on critically examining all the procedures in translational research of any cutting-edge technology paying particular attention to the rectification of existing loose ends and blind spots in current practice. Finally, the discussion of various limitations of this study also indicates specific areas that require further research and scrutiny.

Discussion of results

The results of this doctoral research are based on the insights obtained from in-depth interviews with 46 key respondents from Europe and North America who were involved in planning, conducting or reviewing FIH trials in nanomedicine. There is a significant diversity in the definition of nanotechnology and nanomedicine and it impacts translational nanomedicine. This was discussed in detail in chapter three. Nanoparticles are unique in two aspects: the size of particles in 'nano' scale and the unique properties materials exhibit at that size[1]. Nanomedicine is understood as application of nanotechnology in the field of medicine. However, there is no consensus on what sizes define nanoscale in medical applications[2]. The upper limit of nanoscale in a general discussion of nanomedicines varies from 100nm[2], 300nm[3] up to 1000nm[4], which creates challenges for ethical assessment, regulatory review, toxicity assays and patent examinations[5].

Translational research of any cutting-edge technology involves a number of challenges. Respondents of this study highlighted three main challenges: financial, ethical and drug regulatory that are all discussed in chapter four. The scientists working in universities and small and medium size enterprises (SMEs) highlighted their struggle to obtain the required funding to initiate FIH trials. Therefore, it is worth exploring the constructive role large pharmaceutical industry and philanthropic organizations can play in financing early translational research. However, it is equally important to consider strategies for strengthening drug regulatory and ethical review processes in nanomedicine in low-resource countries.

The term 'nano' is closely linked with the hype about its potential, the hope that it will provide a solution to many health care challenges and fears of potential toxicity[6]. These associations are also reflected in translational nanomedicine. The 'nano' nature of an investigational product is likely to be highlighted in grant applications, the drug regulatory process and the publication of results in eminent journals, but is likely to be withheld in patient information sheets and consent forms for FIH trials[5]. As demonstrated in chapter five, inconsistent and convenient use of the 'nano' terminology in trial-related documents is ethically problematic and can significantly influence patients' and the public trust in nanomedicine and drug development.

Another important conflict raised by the responding investigators and ethics committee members involved the process of patient selection for FIH trials of nanomedicines against cancers (chapter six). The current practice mandates enrollment of patients in the last stages of cancer. The stakeholders interviewed in this research project questioned this practice and argued for the inclusion of patients in earlier disease stages to ensure the production of valid and generalizable knowledge from early clinical trials.

Translational research in any cutting-edge technology is also influenced by factors unrelated to the technology. In nanomedicine, these factors could be an unmet need for

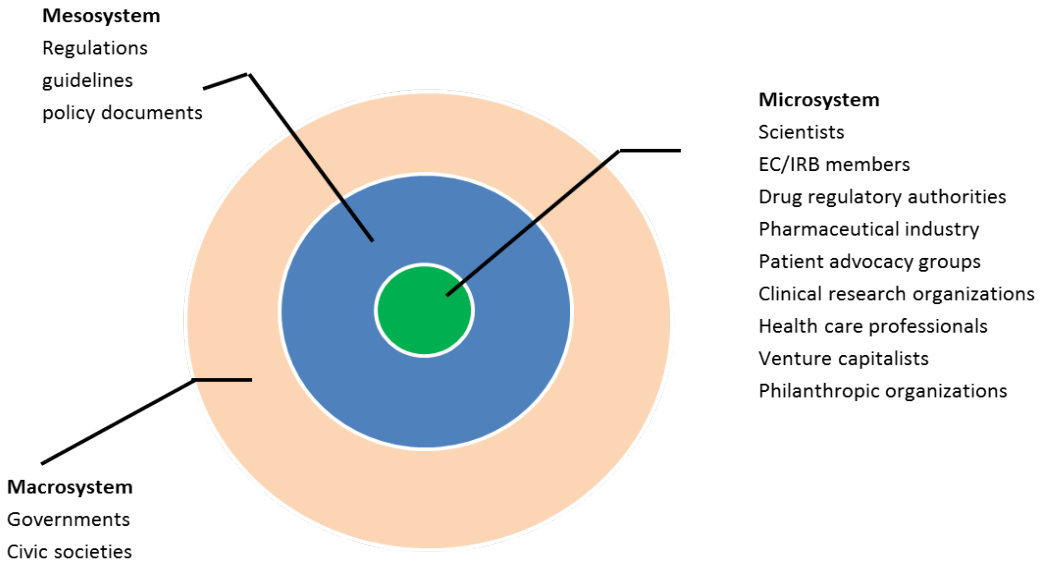
treatment, potential to gain a large market share with a new drug, profitability from a licensed blockbuster or the possibility of having the drug included in health care costs reimbursement from insurance companies. Sometimes, public health emergencies can trigger faster translation of promising vaccine or drug candidates as elaborated in chapter seven. The analysis of accelerated clinical testing of experimental drugs and vaccines during the Ebola epidemic of 2014 is an example. Though vaccine and drug candidates tested in phase I studies during this epidemic were not based on nanotechnology, this case helps understand how a serious epidemic with a high infection and mortality rate and the potential to become a pandemic can trigger an international collaboration and facilitate policy decisions to initiate clinical trials in humans in spite of considerable uncertainty regarding efficacy and the safety of experimental interventions.

National and international guidelines for clinical research also have a significant impact on translational research. A critical analysis of the clinical research guidelines issued by the Indian Council of Medical Research (ICMR) was performed to determine the guidelines' adequacy to regulate clinical research in India and to ensure the safety of human subjects (chapter 8). Though India has been an international hub for clinical trials until recently, the ICMR guidelines do not seem adequate to address research regulation or research subjects' safety.

Ecological model applied to translational research in nanomedicine

The current practice and procedures of the translational research in nanomedicine can be described using the concept of the ecological model developed by Bronfenbrenner in the 1970s to explain human development. The ecological model evolved into a theory over the next few decades and has been used extensively in ecological and public health research and political science[7]. The ecological model has multiple levels or spheres of influencing and interacting factors. The applicability of this model to explain the process of translational

research in nanomedicine became apparent during data analysis. Various actors involved in translational nanomedicine were bound by higher-level structures such as guidelines and regulations put in place by larger entities such as governments and civic societies. The ecological model helped not only in understanding the dynamics among the various actors, but also to identify potential interventions to facilitate translational research in much of cutting-edge medical technology. Three levels (microsystem, mesosystem and macrosystem) of the ecological model critical in translational research in nanomedicine described here help in contextualizing the insights obtained from this research within a larger socio-political-economic and regulatory environment.



1. Microsystem.

The microsystem is the core of the ecological model and in this study it includes the stakeholders who are directly involved in translational research in nanomedicine. They are researchers, investigators, health care professionals, clinical research professionals, ethics committee (EC)/institutional review board (IRB) members, drug regulatory authorities, funding bodies, patent authorities, pharmaceutical industry, patient advocacy groups, academic research centers and patients. This list is not exhaustive, but these were the key

stakeholders identified while mapping the field of translational nanomedicine for this research project. Though these groups can be viewed as 'actors' in translational nanomedicine in various combinations and roles, they do not operate independently of each other or out of context from the recommended or mandatory regulations and guidelines.

2. Mesosystem.

The various guidelines and regulations that control and shape the practices of actors in translational nanomedicine (described at the level of microsystem) constitute the mesosystem. Again, only a few guidelines and requirements are mentioned here as examples and the list is not exhaustive. Mesosystem includes drug regulatory guidelines, national and international ethical standards, social policies that define and influence the focus on a particular technology or disease, guidelines regulating drug pricing, rules regarding cost reimbursement by health insurance companies, regulations related to work place safety and environmental protection, diagnosis and treatment protocols issued by various medical organizations and hospitals, and professional codes of conduct for each professional 'actor' identified in the microsystem. This research did not involve a critical examination of all the potential regulations that shape translational research in nanomedicine as this would require an independent research project.

3. Macrosystem.

The macrosystem is the largest sphere of influence in terms of scope in the ecological model; however, it is also the farthest from the direct influence of the actors (microsystem) in translational nanomedicine. This sphere generally includes civic societies and is influenced by political and economic environments. Strategies to create an active public support for translational research would be situated within the macrosystem and include: public engagement, transparency in scientific communication, facilitation and protection of integrity in scientific research and safeguards for public trust in science and technology. But there are

number of threats to nurturing and building public trust in science and clinical drug development and these also fall in the macrosystem. Our research points to some of these threats, but a more extensive examination would require further investigation.

It is important to note that there is a constant interaction not just among the actors at a particular level, but also between the actors from all levels of the model. For example, regulations and guidelines from the mesosystem clearly influence the actors in microsystem, however, the same actors are also involved in influencing these regulations and guidelines. Civic society's political and economic orientations clearly influence the mesosystem and indirectly the microsystem, but both the mesosystem and microsystem can also potentially influence civic societies. This is a dynamic model and should be flexible in order to incorporate new insights obtained from research and technological development, and the newly identified needs of a specific patient population or a professional body. Dialogue and collaboration across these levels and effective communication among the members of each level is critical for timely and appropriate translation of promising new technology towards achieving society's greater goals of health and human well-being as well as environmental safety and protection.

The results from this research project explained in the beginning of this chapter mainly shed light on various challenges faced by the stakeholders who represent the microsystem. What follows further encompasses discussion on the role of regulation in facilitating or blocking translational research in nanomedicine, thus reflecting on the mesosystem of the ecological model. Final discussion on active engagement of the 'public' in regulatory debates and strengthening the trust in science and technology relates to the macrolevel of the ecological model and requires further investigation.

Need for regulating nanotechnology

Nanotechnology—a key constituent of converging technology[8] (nanotechnology, biotechnology, cognitive science and information technology)—is capable of influencing many aspects of life from medicine to energy production. Each application of nanotechnology (e.g. medicines, electronics, cosmetics, food industry, and aeronautics) raises unique (although not necessarily new) issues that warrant ethical and regulatory discussion. Potential harms caused to workers in the nano-electronics industry[9] generate different concerns than exposure to nanoparticles used in food packaging in terms of the impact, severity and the current regulatory oversight. Similarly, when nanotechnology is used for human enhancement[10], combat warfare, military research, or the creation of super-soldiers[11], it raises specific ethical and societal concerns. The dual-use potential of nanotechnology to create highly virulent pathogens with modified route of transmission to be used as biological weapons must also be accounted for when discussing nanotechnology's impact on health and the environment[12]. Ideally, each of these areas of nanotechnology should be governed by specific regulatory oversight; however, these areas are beyond the scope of this research project, which focused mainly on impact of nanotechnology on health and medicine.

It is often noted that the use of nanotechnology in drugs and medical devices is a highly regulated process compared to other fields in which nanotechnology is used[13]. Yet, the general public is more concerned about the health risks of nanoparticles used in medicine and tends to ignore their exposure to various kinds of nanoparticles in everyday life such as automobile exhaust, dust generated by printing, fabrics and clothing that resists stains, paints used in buildings to resist dust, and the use of nanoparticles in toothpaste to whiten the teeth[14]. The application of nanotechnology in cosmetics, food packaging[15] and as food additives is also regulated to some extent (although usually not as rigorously as medicines). One can buy and use cosmetics or food products off the shelf in a supermarket without the supervision of a

particular authority, whereas nanomedicines can be bought and used only with the valid prescription by a treating physician. Another distinction between the consumption of nanotechnology-based food additives and medicines is that food is consumed by people (young or old) in comparatively higher quantities and over a prolonged period of time whereas most nanomedicines are consumed by the patients for the short duration of their illness. This influences a person's exposure to nanoparticles in terms of quantity and duration, both of which are clearly linked to toxicity and harm[14].

Making generalized statements regarding the risks and potential toxicity of nanoparticles or regulating or de-regulating nanotechnology can prove dangerous since nanotechnology encompasses various sub-fields that imply risks of varying types and magnitude. Hence different applications of nanotechnology are regulated at specific levels of caution[16]. The nuances of debates on nanotechnology regulation can be especially challenging for the general public who may not be familiar with the technical details of nanotechnology or its potential risks. Thus, the public can develop misleading or even erroneous perceptions about the risks and potential of nanotechnology that can significantly influence their acceptance of nanotechnology[16,17]. This is an intersection between the factors in the meso and the macrosystem and requires a careful deliberation and active engagement between societies and scientific communities. Regulations alone cannot speak to the public, but the scientists and the policy makers who are instrumental in drafting regulations and the policy guidelines can create a meaningful dialogue with the public, explain science in simple yet accurate ways and include the public's concerns in their policy deliberations[18].

Nuances in regulation of nanomedicine

Although many legislators and researchers agree that nanomedicine should be better regulated because of its direct impact on the health and well-being of populations[19-22], it is important to tease out various types of risks and ethical challenges underlying these medicinal applications

and ways in which they are being currently regulated. The sections below summarize two key components of nanomedicine and demonstrate the need for the distinct approaches in risk assessment and appropriate regulations.

1. Diagnostic tests

Diagnostic tests with nanoparticles include in-vivo tests, where the nanoparticles enter human body, or in-vitro tests where only a sample of human tissue or blood is in direct contact with nanoparticles in a laboratory[1]. This basic distinction clarifies that in-vivo diagnostic tests require more rigorous testing and safety assurance before being approved for clinical use. The clarity on interaction of nanoparticles inside the human body is critical in this regard. It is also essential to demonstrate how the nanoparticles are metabolized and excreted from the body and the potential risks that could result from their accumulation in a person's body over long periods of time. An example of an approved in-vivo diagnostic test using nanoparticles is a contrast agent containing superparamagnetic iron oxide nanoparticles (SPIONs) used in imaging studies. The use of SPIONs enhances the quality of imaging studies, and enables specific detection of cancer cells or inflammatory cells. The regulatory approval of SPIONs as a contrast agent relies on the fact that the iron oxide nanoparticles are completely broken down by the body and excreted.

A breakthrough in in-vitro diagnostic tests using nanotechnology derives from the possibility of miniaturizing the testing process[2]. This would also decrease the amount of required reagents, while simultaneously improving the test's sensitivity and specificity. The possibility of building a test kit that could simultaneously measure multiple parameters or identify multiple pathogens using a single drop of blood is being investigated. These devices could be extremely valuable in a field setting where sophisticated laboratory facilities or trained technicians are not available[1]. This approach to in-vitro testing could decrease health disparity between low-resource and high-resource countries. Unfortunately, prompt and

accurate diagnosis alone does not address all the health care needs of a population. It is ethically questionable whether or not persons in low-resource countries should be diagnosed with multiple pathogens or blood abnormalities if no treatment is then made available.

Finally, nanotechnology will be critical for developing lab-on-a-chip (LOC) devices[1] that can continuously monitor certain blood parameters (e.g. blood sugar[23]) and relay the information to the patient or to the nearest health center in cases of medical emergency. LOC devices could also store basic health-related information about an individual on a nanochip that could be read electronically by health care personnel in an emergency setting[1]. Nanochips could help identify a person brought to the emergency department in an unconscious state and assist physicians with vital medical history and allergies to medication. LOC technology could improve the monitoring of certain health conditions, but its widespread use in health systems is still far in the future[1]. LOC technology raises questions about individuals' privacy, confidentiality of their health-related data, and access to this data. These concerns are not unique to nanomedicine, since they have been raised before about electronic health data[24-26] and direct-to-consumer genetic testing[27-29].

The improved sensitivity and specificity of diagnostic tests is an advantage for detecting diseases or complications early and treating them effectively at lower costs. However, when test sensitivity increases too much, it also challenges our understanding of what it means to be healthy or to have a disease[10]. The detection of a few cells from solid organs with early cancerous changes in peripheral blood sample by nanodiagnostic tests does not necessarily imply that the person has a cancer or would develop a cancer in next few years. At the moment, there are no set standard diagnostic protocols or definitions that could be used to differentiate between the results indicating a significant finding to warrant medical intervention and situations where further monitoring is needed[10]. Where should the boundary be drawn between when to intervene and when to observe a person for progression to the

earliest signs of a cancer actually developing? It is possible that an excessive reliance on highly accurate diagnostic tests will lead to over diagnosis, over treatment, and cause more stress and psychological harm to individuals who are diagnosed with a disease that might never actually develop. Adapting nanodiagnostic devices in routine health care services without debate, established standard protocols for their use and education of the physicians and the patients on their significance will only create a further medicalized society and medicated population[30].

2. Therapeutic modalities

Nanotechnology enables the development of highly targeted drug-delivery mechanisms that require small drug doses and hence reduce treatment costs, otherwise known as nanotherapeutics[31]. Targeted drug delivery is expected to decrease side effects and provide better treatment outcomes. However, nanotherapeutics also encompass a large variety of technological platforms[3] ranging from liposomes, micelles, gold or silver nanoparticles, carbon nano tubes (CNTs) to multistage vector assembly with silica particles "that deliver therapeutic cargo in sufficient quantity to a target lesion to enable a selective effect"[32]. Each of these technological platforms has unique advantages and risks. Additionally, each platform is at a specific stage of development and approval by drug regulatory authorities; therefore, there is a varying quality of evidence and experience with the safety of these platforms. Liposome based drug delivery mechanism is discussed below to demonstrate the case.

Liposomes are the most extensively studied drug delivery methods using nanoparticles that are approved and available on the market today[33]. Liposomes are phospholipid shells with a surface coating of specific targeting receptors and filled with already-approved anti-cancer drugs. Liposomes have existed since the 1960s, but were re-labeled as nanomedicines in the beginning of the 1990s, when the field of nanomedicine experienced growing scientific interest and funding opportunities. Doxil became the first liposomal formulation to be

approved as a nanomedicine in 1995[34]. Since then, various liposomal preparations have been under investigation and in use. Phospholipids are normal constituents of human cells and therefore, their preparation with already-approved anti-cancer drugs raises fewer questions related to their safety and risk.

In recent years, scientists began exploring other nanotechnology platforms to facilitate targeted drug delivery such as polymer micelles, gold and silver nanoparticles, iron oxide nanoparticles, CNTs and silica vectors[35]. These platforms and the nanoparticles they contain raise a number of questions related to safety and long-term toxicity. Gold, silver, carbon and silica particles are foreign to the human body. When these particles are used in nanoformulations, they have unique physical, chemical and magnetic properties that contribute to the desired therapeutic response. However, the same properties also increase their reactivity in biological systems and their potential to cause tissue damage. CNTs are particularly worrisome due to their micro-needle structure that is similar to asbestos particles and thus, have the potential to cause carcinogenic changes in the human body[36]. The human body does not have metabolic pathways to effectively break down gold and silver nanoparticles or CNTs into safe end products and completely excrete those in a short period of time. Thus these particles are likely to accumulate in a body for months and years and continue to cause cellular irritation and inflammation. Due to their nano size (from a few nm to few hundred nm), these particles can enter deep tissue spaces (deep brain structures, retroperitoneal growths, deep seated liver abscesses) and cross biological barriers (e.g. the blood brain barrier) that normally act as protective mechanisms by restricting the transport of larger particles (biological which are therapeutic substances derived from biological sources, larger drug molecules)[12]. Thus, the very attributes that make nanoparticles attractive as a therapeutic option to treat certain diseases, also create a concern for long-term accumulation and associated toxicity[5].

Finally, there are concerns about the reliability and validity of a battery of tests used to study the toxicity of investigational drug molecules comprised of nanoparticles[37]. Not all nanomedicines can be fully and adequately characterized for safety and toxicity due to inherent limitations of traditional toxicity assays used for testing particles that are not at a nano-scale. For example, iron oxide particles in bulk iron oxide, colloidal iron solution and SPIONs have specific physical, chemical, magnetic properties. So the tests that might work for characterizing colloidal iron dextran solution do not work for SPIONs. Over last few decades, the US National Nano Characterization Laboratory (NCL) has systematically developed tools to conduct characterization of investigational medicinal products using nanoparticles[38,39]. European Union has also focused on developing nanocharacterization capacity in Europe by facilitating active collaboration with NCL.

The risks and safety of an investigational molecule are normally tested in animals before clinical research in humans is initiated. Unfortunately, animal studies have limited reliability due to their study design (lack of randomization of animals, no blinding of investigators), the small number of animals tested, and the limited reliability of disease models produced in animals[40]. Even if there is a biological similarity between a particular animal model and human physiology, the animal studies may fail to detect risks that only manifest in humans. The animal studies may also detect risks and benefits in animals that may not occur in humans[41]. Furthermore, animal studies are highly limited for measuring chronic toxicity since the animals cannot be kept alive and monitored for adverse events beyond a certain period of time (generally few weeks to months).

Despite all these limitations in currently used toxicity assays and preclinical research, each class of nanotechnology-enabled medicines deserves thorough investigation to prove their potential for human health and well-being for reasons described below. However, it is critical that the scientists and investigators reflect on these limitations before initiating human

trials and the ethics committees carefully assess high level of uncertainty inherent in preclinical research in order to protect human research subjects.

Unmet need for treatment

An unmet need for treatment is often the driving force to test new drug options especially when patients' standard treatment options have been exhausted or the side effects of existing treatments are unbearable. Cancers are particularly salient in this regard[31]. Many cancers (e.g. cancer of lungs, ovaries and pancreas) do not currently have effective treatment. Most patients diagnosed with these cancers do not survive more than a year or two and may not even get an opportunity to try existing second-line chemotherapy. Therefore, if CNTs can facilitate drug delivery to one of these cancers and extend life expectancy by a few years, patients might consider the risks and uncertainty related to the long-term accumulation of CNTs in their body to be of a lesser concern (than patients with other cancers and a longer life expectancy) and might accept such a treatment option[12]. This example points out to the need for meaningful engagement with patients while discussing regulation and scope of translational research. Patients' experience of the disease and associated suffering can influence priority setting in research agenda, risk assessment during the ethical review and resource mobilization for supporting translational research.

Duration of treatment required.

Cancer was targeted for nanomedicine development from the start for two reasons. The concern about unmet treatment need was described above and the second reason is that a patient with cancer takes drugs for a shorter period of time (until remission, worsening of condition or death) compared to a patient with a chronic life-long condition (e.g. hypertension, diabetes, HIV). Chemotherapy regimens are often limited to certain number of treatment cycles, so risks associated with long-term exposure to nanoparticles is not a

pressing issue for these patients, especially if a patient's life expectancy is short and the cancer's fatality rate is high. However, this situation changes when nanomedicines are considered for other chronic diseases with no known cure, high disease-related morbidity and requiring treatment till the end of life (e.g. HIV[42], metabolic diseases such as diabetes[43], cardiovascular diseases[44]). One example is an insulin delivery mechanism across the buccal membrane that is being investigated as an alternative to injectable insulin for patients with type II diabetes. Trans-buccal insulin delivery is facilitated by gold nanoparticles that have been proven safe in short-term animal studies. Unlike patients with cancer, patients with diabetes who begin consuming trans-buccal insulin at the age of 40 will be expected to continue its use for next 30-40 years. Current toxicity assays do not provide sufficient information about the safety and chronic toxicity of gold nanoparticles accumulated in a patient's body. Therefore, the advantages of improved control of blood sugar and the prevention of diabetes-related complications must be balanced against the potential long-term toxicity due to accumulation of gold nanoparticles in a patient's body, which remains highly uncertain at this moment.

Route of administration of nanomedicines

The toxicity of nanoparticles in a particular drug delivery platform depends heavily on the route of administration/exposure[45]. This is particularly true if the medicine is injected locally into a lesion and is expected to remain at the site till the end of patient's life (unlike nanoformulations injected intravenously in systemic circulation). In the early 2000s, the European Medicines Agency approved a treatment platform for glioblastoma multiforme- a highly aggressive cancer of brain with no effective treatment options and which kills patients within a year of diagnosis. This new treatment modality includes a visual technology-guided injection of iron oxide nanoparticles into the brain tumor and externally induced focal hyperthermia to ablate the tumor with heat[46]. The iron oxide nanoparticles injected into the

tumor are not expected to be metabolized or excreted by the body, but rather remain localized at the site of injection. The advantage of this approach is that the tumor can be reheated externally in cases of recurrence or growth. Once again, the toxicity of the nanoparticles in a patient with this brain tumor must be weighed against the aggressive cancer, the lack of other effective treatment and the restricted potential of iron oxide nanoparticles to cause systemic toxicity due to their localization within tumors.

Based on analysis of examples above, an argument is made for a case-by-case discussion on each type of nanotechnology-based drug-delivery mechanism to address the safety, toxicity, reliability of animal disease models and the validity of toxicity studies. No treatment modality should be rejected outright or favored without an analysis of the larger context of all the procedures required for the drug's development and approval and patient-related factors such as diagnosis, prognosis, and expected impact on the patient's quality of life.

Need for a critical examination of current regulatory and ethical reviews

The approval and licensing of medical devices, diagnostic tests and drugs requires meeting various regulatory standards, but that doesn't mean that all regulatory issues of nanomedicines have been addressed. Referring back to the various guidelines and regulations that constitute the mesosystem in the ecological model, drug regulatory and ethics review guidelines form a tiny part (albeit critical) of overall regulation of medical nanotechnology. A regulatory approach is needed that is flexible and evolving along with the technology and which includes comprehensive assessment of each category of nanomedicinal products on an individual basis within the limits of available evidence regarding uncertainties, unknowns and ignorance related to potential risks. Furthermore, a critical examination of the adequacy and rigor of the existing review processes in drug regulatory systems is also required to safeguard patient safety and to provide them with effective and affordable treatment options. One area that

definitely needs closer and critical attention is the examination of preclinical evidence (evidence from studies in cell cultures and animal models) on which decisions are based to launch FIH trials. At this moment, it is not clear who (drug regulatory authorities, ethics committee members), if anyone, is carefully examining this preclinical evidence[47].

The second important question is: do ethics committees have necessary expertise and data available to make a thorough assessment of preclinical evidence? Not all animal studies are published in peer-reviewed journals and this is especially true for studies with negative results that might be intentionally withheld from publication[48]. In this context, it is important to create a system where all relevant preclinical data and animal experiment reports are made available to the ethics committees as well as drug regulatory authorities irrespective of positive or negative results so they do not rely solely on the investigators to provide comprehensive preclinical evidence.

Many classes of nanomedicines deserve long-term post marketing to systematically gather safety and chronic toxicity data[49]. In the light of unmet patient needs, it is understandable that certain drugs are approved and licensed based on limited existing evidence. However, one way to strengthen post-marketing surveillance could be to provide conditional licenses, assign a few experts in each country or region to treat patients with the new drug and meticulously collect safety data before allowing all physicians to prescribe the drug. Which physicians should be selected for the initial limited and conditional licensing phase of a particular drug requires further discussion, but this approach could strike a balance between the patients' unmet treatment needs and the systematic collection of evidence to ensure drug safety.

Public and patient engagement: Strengthening the macrosystem

Finally, patient engagement is particularly important when discussing regulation of nanomedicine and so is the inclusion of the general public in debates related to regulation of nanotechnology[50-52]. It is challenging to determine who should represent patients or the public, and exactly what role these two groups should play in translational research in general, and not just regulation of a particular technology. Within the macrosystem, inclusion of the public voice and needs in social debates on the regulation of any technology (particularly so with medical technology) is critical for building public trust in science, technology and the regulatory mechanisms[53]. Without the public trust, no technological field can truly harness its full potential and risks being rejected by the same population that was envisioned as the potential end user. This point highlights an interaction between the mesosystem (regulation and policy) and the macrosystem (the public). There is an urgent need to develop strategies to strengthen the relationship among the stakeholders of translational research (microsystem), those who create regulatory policies (mesosystem) and the general public (macrosystem)[54]. These relationships must be built on trust, honesty and open communication. The findings of this exploratory empirical research have highlighted the complex and interconnected challenges and interactions of multiple stakeholders in translational nanomedicine. Further research investigating specific influence of factors at the meso and the macrosystem will be instrumental to find solutions to those challenges.

Limitations and implications for further research

This exploratory study has methodological limitations to be considered while discussing the results. First, the results of this qualitative study focus mainly on the microsystem of the ecological model presented here and should not be interpreted without considering the influence of the mesosystem and the macrosytem. These results point to key concerns that need further scrutiny but conclusive inferences cannot be made. The heterogeneity of study sample in terms of location, professional background and role of respondents also limits the generalizability of the results even though the study successfully demonstrated the broad scope of concerns related to translational research in nanomedicine. Our sample had a low representation of ethics committee members and drug regulatory authorities whose insights are critical to understand the complete picture of challenges in ethical and drug regulatory review of FIH trials with any cutting-edge medical technology. These methodological limitations were discussed in greater depth in chapter two. The results of this study will definitely help refine the research questions further so that greater insights can be obtained from a homogeneous sample of particular stakeholders. For example, a survey questionnaire designed to elicit challenges in the translational research in nanomedicine for ethics committee members or drug regulatory authorities will help gather insights from multiple countries and facilitate an examination of the influence of political and regulatory environments in translational research. As pointed out earlier in the discussion, exhaustive analysis of all possible regulations and guidelines and a comparison of their impact across various national jurisdictions would be valuable to better understand the challenges in translational research. Finally, drug development is a highly profit-driven activity involving multiple stakeholders with conflicting goals and interests. It is important to bear in mind that public trust in science and drug development is also crucial to facilitate translational research in medicine. Trust is a subjective concept, often assumed to be present without a full analysis

of the various threats to it. An investigation to examine the role trust plays in translational research and drug development and to develop strategies to safeguard trust in the system is highly recommended.

Conclusions

The aim of this exploratory research project was to describe the challenges in translational nanomedicine with a particular focus on FIH clinical trials. In-depth interviews with key stakeholders were conducted to understand these challenges. Main results of this study indicate that there is diversity in the definition of nanomedicine and it adversely influences the translational research. Ethical, financial and regulatory challenges in initiating FIH trials need to be addressed at a systemic level than at the level of stakeholders themselves. Stakeholders are divided in their opinions regarding the explicit mention of the 'nano' nature of investigational molecule in IC forms. They also challenge the current practice of including patients with end stage cancer and no treatment options as trial participants in FIH trials. Contextual factors such as public health emergencies can trigger accelerated translational research and initiate testing of experimental interventions in human beings in spite of significant uncertainty related to the risks and safety.

These results mainly describe the challenges at the microlevel and point to the interventions that could facilitate the translational research in nanomedicine. The role of trust in scientific research and the meaningful public engagement deserves further investigation to gain the complete picture of challenges in translational research in nanomedicine. Discussion on regulation of a new technology often hinges on the types and the severity of risks the technology might cause. Though nanomedicine does not raise new ethical questions, the ethical questions resurfacing in its context require a case-by-case analysis of each product and a focus on loose ends and blind spots in current regulatory mechanisms. An active engagement of the public and the patients in the translational research will help in building

public's trust in science and drug development and facilitate their acceptance of nanotechnology to address health care needs and to minimize the health disparity and inequality between various countries.

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Appendices

Ethical issues of cutting edge biotechnology: embedded interdisciplinary risk benefit evaluation of first-in-human trials in synthetic biology and nanomedicine.

Interview guide for Nanotechnology experts

Information gathered about the stakeholders interviewed

- Name
- Institution/university
- Present Position/post
- Number of years in this post
- Formal training in which domain: medicine, research, other
- How would you describe your current professional profile in relation to nanomedicine and or synthetic biology?

A- **Understanding experts' work/ideology/goals**

1. Please tell me about your current or on-going project/s in nanomedicine and/or synthetic biology.
2. What is the added value of this technology compared with standard existing therapy?
3. Which of your projects is a likely candidate to enter a first in human trial?
4. When do you think this application might be tested on human beings?
5. Are there similar projects which have already entered first in human trials or are early candidates for these trials? Can you tell me more about them?

B- Assessing the risk-benefit profile of new technology

6. You just described various potential applications of this technology for human health and well-being. What other aspects (direct and indirect) should we keep in mind when we are discussing this technology?
7. What limitations do you consider important at this moment regarding this technology?
8. How do you plan to address these limitations?
9. Can we address all the limitations? If not, which limitations are acceptable given the advantages of the technology? In what circumstances do you think these limitations are compatible with starting an FIH trial?
10. What are the potential risks we have to keep in mind in regards to the application we have been talking about?
11. As an expert in this field, what differences do you perceive in risks posed by nanomedicine and synthetic biology as compared to other drugs or medical technologies?
12. In your opinion, do we have to be more careful or vigilant while assessing the risks of these technologies compared with other technologies or medicines?
13. In current practice various tools are used for risk assessment, like animal studies, efficacy and toxicity studies. Can the same tools be used for this new technology?
14. If we need some modifications, what kind of modifications would you suggest given the unique nature of this new technology?

C- Facilitating technology from bench to bedside.

15. What challenges do you see in the current system when it comes to bringing lab research to a stage where the first clinical evaluation in humans is started?
16. Have you been part of any project in the past where clinical application was tested as a FIH study? What key insights will you like to share from that experience?
17. Developing clinical applications of cutting edge biotechnology in humans is often an interdisciplinary task. Who in your opinion are the key stakeholders that influence whether a technology will reach a clinical phase? What specific roles do you envision for each of these stakeholders?

D- First in human trials:

18. What motivates you to design a FIH trial?
19. What kind of support/collaborators do you need to plan or implement a FIH trial using this technology?
20. What are the minimum conditions/criteria that need to be fulfilled to enable an FIH trial of this technology?
21. Do you see any special circumstances/factors that might facilitate this technology rapidly entering FIH trials? What will those circumstances/factors be?
22. In this particular example you provided, what challenges do you see in undertaking an FIH trial?
23. What differences do you see between FIH trials for classical drug research and the FIH trials of technology that we are discussing?
24. One of the key components of FIH trials is defining the target group of patients who could be considered for trial participation. For the technology that you are working on, which patients will you want to enrol if an FIH trial is planned? Why?
25. In an FIH trial of the technology that you just described, what benefits do you anticipate for the participants? If there are no benefits to the participants, how would you justify enrolling them into the trial?
26. What safeguards can be built in the trial design to minimize the risks or harms to study participants?
27. Patient safety is often the biggest concern in clinical research, and more so in FIH trials; who in your opinion are the other stakeholders that need to be involved to share this responsibility of patient safety? And in what roles?

E- **Designing and getting ethics committee clearance for FIH trial** (these questions are relevant for only those experts who might have been part of getting ethics approval for FIH trial or for the doctors involved in FIH trials. Since there are very few FIH trials in nanomedicine and synthetic biology, we will probably have to ask these questions in the context of any FIH trial (drugs, other technology)

28. Have you ever been involved in designing a FIH trial or getting ethics committee approval for an FIH trial? In what ways? Can you tell me more about it?
29. What challenges did you encounter in the process of getting ethical approval for this FIH trial?
30. What were the main concerns of the ethics committee while evaluating your proposed trial?
31. How did you address these concerns?
32. How long did the process take?

33. What strategies can you think of to ensure that the evaluation process of FIH trials takes into account all relevant ethical issues and is at the same time efficient (i.e. does not induce undue delays or hamper research)?
34. Who do you think is responsible for ensuring that FIH trials take into account all relevant ethical issues?
35. Who shares the responsibility for resolving all the ethical issues at stake before approving such trials?
36. How do you perceive the role of patient groups being involved in the ethics committee decision making process when FIH trials are being reviewed? What should that role be?
37. What are the strengths and weaknesses of current ethics committee evaluation process for FIH trials? Could you give me some examples?
38. What would an ideal policy for ethical evaluation of FIH trial be like? If you could draft such a policy, what components will you focus on?

F- Implementation of FIH trials (only for those who are involved in conducting such trials. Since there are very few FIH trials with nanomedicine and synthetic biology, we might have to talk to people who are involved in implementing FIH trials with ordinary drugs or medical devices. Here we hope to find out about issues around informed consent, patient recruitment, explaining the design of the trial, risks and benefits to the patients)

39. Who are the study participants best suited to be enrolled in this study, in your opinion? Healthy volunteers, patients with no other treatment options and likely to die as in some form of cancers, or patients with diseases for which the technology is being devised (stable patients)?
40. What challenges do you see in explaining the details of study design to these participants?
41. How do you address these challenges?
42. How do you make sure that the participant has really understood what is at stake before agreeing to be part of the study?
43. To what extent do you think the process of obtaining informed consent in such a trial serves the purpose of respecting study participants' autonomy and safeguarding their interests?
44. It is often a challenge to provide comprehensive information about the study design and an objective overview of the risks and benefits associated with it. How do you think we can provide such detailed information and at the same time recruit the required number of suitable trial participants in a timely fashion?

I sincerely thank you for your time and all the inputs. Would you like to receive and read the transcripts of the interview? Is it ok if I contact you again in case, I have few new questions or need some more clarification? Please feel free to contact me again, in case you have some other thoughts/insights on this topic. I will be more than happy to incorporate those in relevant sections of this interview.

Ethical issues of cutting edge biotechnology: embedded interdisciplinary risk benefit evaluation of first-in-human trials in synthetic biology and nanomedicine.

Interview guide for ethics committee members/ethicists

A- Information gathered about the stakeholders interviewed

1- Name
2- Institution/university
3- Present Position/post
4- Number of years in this post
5- Formal training in which domain: Philosophy, medicine, science and technology studies, public policy, other

B- Understanding Specific contribution to ethics of nanotechnology and or synthetic biology(for the ethicists who have published on nanotechnology and synthetic biology)

6- Please tell me about your contribution/work in relation to nanotechnology and or synthetic biology.
7- How long have you been working on these topics?
8- What made you interested in this topic?
9- How has this interest evolved over the years?
10- Please tell me the words that come to mind in response to “nanotechnology” and/or “synthetic biology”.
11- In your opinion, what ethical issues are especially important with regard to nanotechnology and synthetic biology? Please give me examples.
12- What makes these particular issues so important?
13- What potential do you see in nanotechnology and synthetic biology for improving human health and well-being?
14- What aspects of these technologies, particularly their human application, make you concerned?
15- Let us consider first in human trials with nanomedicine or synthetic biology. How would you describe them if you compare them to other FIH trials for example cancer drugs?
16- Many ethicists have argued that nanomedicine and synthetic biology do not pose any new risks to human beings and hence existing ethical guidelines and principles should be used to assess these technologies. What is your opinion about this?
17- Depending on the opinion expressed in question above, the follow-up question will be how these technologies and FIH trials should be evaluated.
18- One of the concerns is that the existing ethical guidelines for FIH trial do not provide specific guidance to evaluate FIH trials in naomedicine or synthetic biology. What is your opinion on this? Is there a need to develop new ethical guidelines and international policies for FIH trials of nanomedicine and synthetic medicine?
19- What components are essential in these new guidelines and policies to ensure that they are accepted by the international community, and ensure that they provide concrete guidance for decision makers (ethics committee members, policy makers and regulatory bodies)?
20- In your opinion, which stakeholders are crucial in drafting such new guideline?

21- In your opinion, how can these guidelines be enforced?

C- Ethical evaluation of FIH trials in synthetic biology and nanomedicine.(These questions are for Swiss and International research ethics committee members who might have been involved in evaluation of FIH trials in general and if possible for nanomedicine and/or synthetic biology.)

22- Please tell me about your work as a member of ethics committee. How long have you been working on this committee and in what roles?
23- Have you been involved in evaluation of FIH trials of synthetic biology or nanomedicine?
24- The following questions are intended to elicit your individual opinion/perception regarding ethical evaluation of FIH trials. Please, describe to me the process of formulating your own position in the example you provided above.
25- What factors did you focus on during evaluation of this FIH trial?
26- What challenges did you face (in the provided example) while formulating your own position?
27- How did you argue and justify your own position (in the provided example)?
28- The risk-benefit balance is often considered crucial in ethical evaluation of research projects. But it is not always clear how each individual ethics committee member understands and defines what risk is and what benefit is. Please tell me your understanding/definition of risk using the example that we have been taking about.
29- Similarly please tell me how do you define/describe/understand benefit in the context of the FIH trial that we are discussing.
30- Literature often points out that ethical evaluation is a highly intuitive and hence subjective process both at the individual member level and even as a committee. What is your opinion about this?
31- How much role does intuition play in your own decision making process when it comes to ethical evaluation of research proposal?
32- What other factors did you consider while evaluating this particular FIH study?
33- What objective tools, guidelines models/strategies could be helpful to assist the ethics committee members while reaching a final decision? You might have some real examples from your own work as an ethics committee member which might shed light on this issue. Please share that example with me.
34- What is your opinion on the utility of existing ethical guidelines and policy documents for evaluating FIH trials?
35- What are the positive contributions of these guidelines and policies?
36- What is missing from these guidelines?
37- One of the concerns is that the existing ethical guidelines for FIH trial do not provide specific guidance on evaluation of FIH trials in naomedicine or synthetic biology. What is your opinion on this?
38- In the UK, they have special ethics committees to evaluate FIH trials of gene therapy. What do you think about this?
39- Let us now focus on the evaluation process of the FIH trial that we are discussing in the ethics committee setting. Please tell me how the committee reached a final decision when members disagreed on various aspects of the trial under consideration?
40- In this FIH trial, which aspects/ethical issues were an absolute priority and hence non-negotiable when it came to ethical approval?
41- How long did it take to make a final decision?

42- Do you have any examples when, even after significant discussion and deliberation, the members could not come to a conclusion? What was done in that case to facilitate a final decision?

43- It is often said that ethicists are too cautious with new technologies and that delays progress of scientific technology. What is your opinion on this?
44- What are some aspects of current ethical evaluation process that you think need to be modified to optimize ethical evaluation of FIH trials?
45- In the trial that we have been discussing, in your opinion, who are the best participants for enrollment in FIH trials?
46- What makes them the ideal candidates for trial participation in this case?
47- In your opinion, under which circumstances is it justifiable to allow patients to be part of an FIH trial when there is no likely benefit but the risks are quite significant? Please describe at least one theoretical or practical example where this is the case.
48- Involvement of patient group representatives as ethics committee member has been encouraged in recent years to bring patient perspectives to the discussions. What role do you see for involving patient groups in ethical evaluation of FIH trials?
49- Do you have any examples from your own experience or from the literature where patient participation in RECs was attempted? How was that perceived?

I sincerely thank you for your time and all the inputs. Would you like to receive and read the transcripts of the interview? Is it ok if I contact you by email if I have any new questions or need further clarification? Please feel free to contact me again, in case you have some other thoughts/insights on this topic. I will be more than happy to incorporate those in relevant sections of this interview.

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Education

02/ 2016 **PhD in Biomedical Ethics (Dr.sc.med.),**
University of Basel, Switzerland.

06/ 2011 **Erasmus Mundus Master's in Bioethics (EMMB),**
Katholieke Universiteit Leuven, Belgium, Radboud Universiteit Nijmegen, Netherlands and Università Degli Studi di Padova, Italy.

08/2010 **Master's in Medical Anthropology (MSc),**
University of Amsterdam; Netherlands.

01/ 2007 **Master's in Public Health (MPH),**
James P Grant School of Public Health, BRAC University; Dhaka, Bangladesh.

01/ 2003 **Bachelor of Medicine and Bachelor of Surgery (MBBS),**
Mumbai University; India.
Medical License no: 2352, Maharashtra Medical Council, India

Academic awards and achievements

02/ 2016: summa cum laude, PhD in Biomedical Ethics
06/ 2011: summa cum laude, Erasmus Mundus Masters of Bioethics.
08/ 2010: magna cum laude, MSc in Medical Anthropology, University of Amsterdam.
01/ 2007: magna cum laude, MPH, BRAC University, Bangladesh.
01/ 2003: Homrasji Kama gold medal in Obstetrics & Gynaecology, Mumbai University.
1997-2001: Recipient of Sir Ratan Tata Trust scholarship for Medical Education.

Academic work experience

03/2016 -12/2017 **Postdoctoral researcher** (80%)
Institute for Biomedical Ethics, University of Basel, Switzerland
An exploratory qualitative research on research integrity among researchers in medical sciences and life sciences.

03/2016 -02/2017 **Researcher** (20%)
Institute for Clinical Epidemiology and Biostatistics,
University Hospital Basel, Switzerland
Qualitative research project to investigate reasons and implications of discontinuation of clinical trials due to slow or low participant recruitment in Switzerland, Germany and Canada.

09/2012-02/2016 **PhD candidate**
Institute for Biomedical Ethics, University of Basel, Switzerland.

Project management

- Managed an interdisciplinary research project in empirical bioethics
- Conducted 48 qualitative in-depth interviews
- Carried out qualitative data analysis with project team
- Contributed to dissemination of the project results through scholarly publications and conference presentations

Teaching

- Taught a seminar on ethical issues of cutting edge biotechnology in fall 2013.
- Contributed to teaching and tutorials in medical ethics at school of medicine.

Grant writing

- Wrote a grant for Indo-Swiss Joint Research Project on ethical issues in cord blood banking.
- Took a lead in organizing 27th International Conference of European Society of Medicine, Health care and Philosophy in Basel in August 2013.

Antelope career coaching program

Was part of the first Cohort of 30 women PhD students from total of 150 applications for newly developed Antelope career coaching program at University of Basel. This tailor-made coaching program aims at encouraging and supporting women scientists to pursue an academic career and involved structured mentorship and personalized coaching sessions.

2011 - 2012 **Lecturer in Public Health**
Windesheim Honours College, Zwolle, the Netherlands

Teaching and coaching

- Taught course in public health, epidemiology, project management and health communication to students of four year international honours Bachelor program in Project Management with specialization in Public Health
- Developed syllabi and course manuals
- Career counsellor for 1st and 2nd year students.

Grants recieved

2016: Käthe Zingg Schwichtenberg Fond grant (CHF 58,784/-) from Swiss Academy of Medical Sciences

2015: Career grant (CHF 30,000/-) from from Niklaus und Bertha Burckhardt-Bürgin-Stiftung

Research experience

2012 – 2016 **PhD research project**

Aim - to document challenges of translational research of cutting edge technology with particular focus on first in human trials of nanomedicine.
Method - *Interdisciplinary qualitative research*
Sample size - 46 in-depth interviews
Funding - Swiss National Science Foundation

2010 – 2011 **Research project for Erasmus Mundus Masters in Bioethics**

Aim - to understand the motivation and decision making process of Dutch citizens who endorsed the public initiative ‘Uit vrij wil’. This initiative aimed at creating political and social debate to amend existing euthanasia legislation in the Netherlands to include life fatigue as a legitimate reason for requesting assistance to die.
Method - *Exploratory qualitative research*
Sample - 11 in-depth qualitative interviews
Funding - Erasmus Mundus Scholarship

2009 – 2010 **Research project for Masters in Medical Anthropology**
Aim - Life story narratives of elderly, middleclass, Indian women married for more than 35 years to understand meaning of love and its influence on marriage.
Method - *Exploratory qualitative research*
Sample - 12 in-depth qualitative interviews
Funding - NUFFIC (Dutch government) scholarship

2006 – 2007 **Research project for Masters in Public Health**
Aim - to understand meaning of 'good care' from the perspective of migrant pregnant women living in slums of Mumbai and seeking obstetric care in publically funded health centres.
Method - *Exploratory qualitative research*
Sample - 10 in-depth qualitative interviews

Professional work experience

2007 – 2009 **Sr. Technical Officer (STI/HIV capacity building team)**
Family Health International (FHI 360) India County Office, New Delhi, India

We worked with 380 specialized STI/HIV clinics across six states with high HIV prevalence and national highways in India providing services to 300,000 people at high risk of acquiring STIs and HIV such as male and female sex workers, injecting drug users and truck drivers.

- Technical consultant and liaison with national and state level government and NGO partners for Syndromic management of sexually transmitted infections (STI), Primary HIV care & treatment, HIV/ STI Counseling and HIV-TB screening in high risk population.
- Provided onsite supportive supervision to the medical, nursing and counseling staff of HIV/STI clinics
- Participated in writing research proposal for operations research to evaluate efficacy of WHO syndromic case management for STIs in vulnerable population, prepared and monitored (logistics, laboratory and medical supplies, training of the site staff) 16 sites for this research across India
- Key trainer for training in syndromic STI case management, primary HIV care, community based TB screening in high risk population for doctors, nurses, counselors at national, state and local NGO partners

2003 – 2005 **Surveillance Medical Officer**
National Polio Surveillance Project, WHO-Government of India collaboration

WHO consultant for polio eradication effort in four districts in two states of Northern India with total population of 11 million.

- Built and maintained infectious disease surveillance network in formal as well as traditional health care systems
- Provided technical support in planning community wide immunization activities with oral polio vaccine
- Monitored supply and cold chain maintenance of oral polio vaccine in the field
- Ensured accurate and timely reporting of immunization coverage

- Trained doctors, pharmacists and nurses for infectious disease surveillance and immunization activities
- Provided regular feedback and suggestions to local governmental partners as well as to state and national level WHO office on performance of the districts on polio eradication
- Managed district level units of WHO National Polio Surveillance Project and team consisting of 20 staff members

On-job trainings

July 2008: **Summer Institute on Sexuality, Culture and Society** University of Amsterdam, Netherlands.

Sep 2005: **International course in Applied Epidemiology** Emory University; Atlanta, USA.

Publications

Peer reviewed research articles

1. **Satalkar P**, Elger BS, and Shaw D. (2016) Stakeholder views on participant selection for first-in-human trials in cancer nanomedicine. *Current Oncology*. 23(6): e530-e537.
2. **Satalkar P**, Elger BS and Shaw D. (2016) Defining nano, nanotechnology and nanomedicine: Why should it matter? *Science and Engineering Ethics.* 22(5):1255-1276.
3. **Satalkar P**, Elger BS, Hunziker P, and Shaw D. (2016) Challenges of clinical translation in nanomedicine. A qualitative study. *Nanomedicine: Nanotechnology, Biology and Medicine.* 12(4):893-900.
4. **Satalkar P**, Elger BS, and Shaw D. (2016) Naming it "Nano": Stakeholders' views on use of "nano" terminology in informed consent forms of first in human trials in nanomedicine. *Nanomedicine*. 11(8):933-940.
5. **Satalkar P**, Shrivastava, S. & De Sousa A. (2015) Internet mediated psychotherapy: Are we ready for the ethical challenges? *Indian Journal of Medical Ethics.* 12(4) 220-227.
6. **Satalkar P,** Elger BS & Shaw D. (2015) Prioritizing healthcare workers for Ebola treatment: Treating those at greatest risk to confer greatest benefit. *Developing World Bioethics*. 15(2) 59-67**.**
7. **Satalkar P** & Shaw D. (2015) Not Fit for Purpose: The Ethical Guidelines of the Indian Council of Medical Research. *Developing World Bioethics.* 15(1) 40-47.
8. **Satalkar P** (2012) To marry or not to marry? Studying others to know myself. *Medische Anthropologie.* 24(1): 207-224.
9. **Satalkar P** (2012) Lost opportunities. *Indian Journal of Medical Ethics* 9(1): 53-56.
10. Mann A, Mol A, **Satalkar P**. et.al (2011) Viscous food and tasting fingers. *HAU: Journal of Ethnographic Theory.* 1(1): 221-243.
11. Selim N & **Satalkar P.** (2008) Perceptions of mental illness in a Bangladeshi village. *BRAC University Journal.* 5(1): 45-55.

Book chapter

- Selim, N. & **Satalkar, P.** (2008) Mental illness perceptions. In: S. van der Geest, N.Selim & S. Zaman (eds) Daily health concerns in Kakabo: Anthropological explorations in a Bangladeshi village. Dhaka: James P. Grant School of Public Health, pp. 53-62.

Book reviews

- **Satalkar, P.** (2014) Book review of Kaebnick G. and Murray T.: 2013, Synthetic Biology and Morality. Artificial Life and the Bounds of Nature. Cambridge, MA: MIT Press. Med Health Care and Philos 17(3): 477-478.
- **Satalkar, P.** (2010) Book review of Akhavi, Negar (ed) AIDS sutra: Untold stories from India. Medische Antropologie 22 (2):433-434.

Peer review

For Indian Journal of Medical Ethics, American Journal of Bioethics, Journal of Empirical Research in Human Research Ethics, Accountability in Research: Policy and Quality Assurance and Nanoethics, Journal of Bioethical Enquiry.

Select conferences, talks, and presentations

- Satalkar P (2015). Balancing the 'global' and the 'local': Case of clinical trials regulation in India. Global Health Bioethics Conference, Oxford, UK. 29th 30th September 2015.
- **Satalkar P**, Shaw D, Elger BS (2013). What is risk anyway? Differential discourse on risk of first in human trials in nanomedicine. International conference of American Anthropological Association, Chicago, United States. 20th -24th November 2013.
- **Satalkar P**, Shaw D, Elger BS (2013). The embryogenesis of nanomedicine: working through ethical challenges of FIH trials. 5th International Conference on pharmaceutical life cycle, Driebergen, the Netherlands. 2nd -5th September 2013.
- **Satalkar P** (2013). Challenges of translational research in medical applications of nanotechnology. International conference for young scholars on research ethics, Hannover, Germany. 26th - 30th August 2013.
- **Satalkar P**, Shaw D, Elger BS (2013). Nano Tech, mega risks? Ethical uncertainties in first-in-human trials of nanotechnology. 27th European Conference on Philosophy of Medicine and Healthcare, Basel, Switzerland. 14th -17th August 2013.
- **Satalkar P**, Genske A, Shaw D, Engel S, Elger BS (2013). Assessment of risks and benefits of FIH trails in nanomedicine-Enquiry through empirical research in Bioethics. 12th Annual IAS-STS Conference "Critical Issues in Science and Technology Studies", Graz, Austria. 6th -7th May 2013.

Poster presentations in Academic Conferences

- **Satalkar, P**; Genske, A; Shaw, D. M; Elger, BS (2013). First in Human (FIH) Trials of Nanomedicine: A fine balance between caution and progress. CLINAM Conference (Clinical Nanomedicine and Targeted Medicine) Basel, Switzerland. 23rd-26th June 2013.
- **Satalkar, P**; Christen, M (2013). Defining and Defying Death: Making Sense of Brain Death and Cadaveric Organ Donation in India, International Neuroethics Society Annual Meeting, San Diego, California, United States. 7th -8th November 2014.

Invited talks

04/2016: Invited speaker debate on ethics of CRISPR/Cas9 at University of Basel.
02/2016: Invited speaker at Life Science, Switzerland (LS2) event on ethics of synthetic biology.
01/2016: Invited speaker at Basel Oncolunch meeting at university hospital of Basel.
03/2015: Invited speaker at monthly PharmaTech meeting of department of Pharmaceutical Sciences of University of Basel.
05/2013: Guest speaker at Windesheim University of Applied Sciences, Zwolle, Netherlands.
03/2012: Guest speaker for the Netherlands chapter of European Youth Parliament