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Perceived risks and benefits of nanomedicine: a case study of an anti-tuberculosis drug

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Abstract

Nanotechnologies are novel and have intriguing properties, and yet they have some potential for harm. Using the case study of a nanoparticle anti-tuberculosis drug, this paper analyses the considerations made by different stakeholders in assessing the potential risks and benefits of nanomedicine. Interview data from patients, nurses, caregivers and scientists from Gauteng province in South Africa were analysed through the lens of the Social Construction of Technology theoretical framework, which emphasises the importance of understanding the influence of social context on the development, interpretation and use of technologies. The stakeholders displayed varying interpretations of the drug based on their vested interests. To the patients, nurses and caregivers, the challenges and they experienced in the treatment of tuberculosis influenced what they perceived to be potential risks and benefits of the drug. The scientists considered the functionality of the drug and its potential societal benefits but were also concerned about side effects. The study reveals that the context of stakeholders matters in their assessment of the risks and benefits of nanomedicine. Thus, it is not sufficient to assess a technology focusing only on its technical properties, but it is important to consider how the technology is nested in its broader social, political and cultural environment.

Keywords: nanotechnology; risks; benefits; balancing; interpretive; flexibility

Introduction

The use of nanotechnology in medicine is poised to revolutionise public health by facilitating targeted delivery of drugs (Schulte, 2005; Bawa, 2008; Ciutan et al., 2010). The ability of nanoparticles to traverse cell walls contributes to ensuring that drugs are delivered where they are needed (Barbu et al., 2009; Pearce et al., 2012). However, the technology is associated with unintended side effects due to the small size of the nanoparticles, which may cause harm to human health and eco-systems in the environment (Preston, 2006; Renn & Roco, 2006; Falkner & Jaspers, 2012). As is the case with most emerging technologies, the risks are as yet poorly understood (Pidgeon et al., 2009). In addition, regulations have struggled to keep up with the pace of scientific innovation in this field (Falkner & Jaspers, 2012). There is a growing public concern from policy makers caused by negative perceptions that nano-enabled products are proliferating uncontrollably and being released without adequate testing of their safety (Wright, 2016).

The current lack of understanding of the risks of nanotechnology hinder meaningful risk assessment (Klaine et al., 2012; Bakand & Hayes, 2016). No accepted test methods or validated data are available to support quantitative estimates of the risks and benefits of nanotechnology applications (Sweet & Strohm, 2006). However, it is not an option to wait for the uncertainties to be resolved before taking steps to manage the risks, because of the growing public concerns about nanotechnology, which are driven by risk perception. What is missing is a more reflexive, incremental, and cooperative approach, both for the management of emerging risks from nanotechnology applications, and for the management future emerging technologies.

Application of the precautionary principle has been encouraged in balancing potential risks and benefits associated with nanotechnology (Lin-Easton, 2001; Weckert & Moor, 2006). The precautionary principle recognises the reality that health and environmental decisions are made in the face of pervasive uncertainty and it urges decision makers to delay new technologies until their safety can be adequately ensured (Marchant & Mossman, 2004). This requirement is often framed as placing the burden of proof on the proponent of a technology to demonstrate its safety. Given the considerable uncertainty about the risks of nanotechnology, the technology appears to be a suitable candidate for application of the precautionary principle. However, the precautionary principle is not a workable model for the management of risks and benefits related to nanotechnology. This is because it fails to provide direction on the critical areas that need to be considered in moving forward with regulatory decisions, such as the level or type of evidence of harm deemed sufficient to trigger the principle, what level of risk is acceptable, and how the benefits of the technology should be weighed against its risks (Wiedemann & Schütz, 2005, Marchant, 2003).

Application of the precautionary principle is prone to arbitrary decision making (Sunstein, 2005). For example, the application of the precautionary principle resulted in the ban of corn flakes enhanced with essential vitamins in the Netherlands, the prohibition of caffeinated energy drinks in France, and the rejection of food aid containing genetically modified corn in the famine-affected

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nation of Zaire (Marchant & Mossman, 2004). The limitation of the precautionary principle is its bias towards maintaining the status quo as this has the effect of hindering new technologies even if they may ultimately prove beneficial for the environment or public health (Cross, 1996; Holm & Harris, 1999).

The emerging discourse on new risk management models for emerging technologies such as nanotechnology often includes expanding the scope of stakeholders beyond only producers and experts (Delgado et al., 2011). As the application of nanotechnology in medicine promises health benefits, engaging different user groups is an inclusive step towards ddemocratic governance of the technology. Using the case of a nanoparticle anti-tuberculosis drug being developed in South Africa, this study addresses the research question: What considerations are made by stakeholders in balancing the potential risks and benefits of nanotechnology?

Since the drug was still confined to the laboratory, the study focused on the technology 'in the making' as espoused by Akrich (1992), to illustrate by means of empirical evidence that the assessment of technologies does not necessarily start when the artifact physically leaves the laboratory for use. Instead, the journey begins when the idea is conceived and the producers start imagining how the technology will be used to solve societal problems. According to Vallejo-Torres et al. (2008), the classical approach of medical technology assessment is to evaluate technologies after they enter the market place. In most cases, the early assessment of technologies is the arena of scientists working on the artifact in the laboratory because of their expertise. While this is important, it is restricted to a few groups of people and it excludes many, especially those who lack the technical knowledge to be engaged in the development of the technology. This paper deviates from that norm by not limiting the early assessment of the technology to the experts, but going a step further to incorporate the views of laypersons who are experts in their own right. The study was meant to facilitate the assessment of the drug at an early stage with regard to its safety and performance, as well as to its future impact on clinical and non-clinical patient outcomes. The research was done in the laboratories where the drug is made, in clinics and hospitals where patients are treated, and in patients' homes. The different stakeholders were assessed in terms of how they conceptualised the drug's potential risks and benefits.

Nanoparticle Anti-tuberculosis Drug

The study is based on a research project aimed at developing a nanoparticle anti-tuberculosis drug in South Africa. The research project is an initiative of the Department of Science and Technology that was conceived in 2002 and involves the use of nanoparticles to target infected cells and enable slow release of the drug while promoting enhanced retention of the antibodies in the diseased cells (Hayeshi et al., 2012). This has the positive effect of reducing the treatment dose frequency from daily to once a week and lessening the total standard treatment time from six to two months, because the actively targeted anti TB drugs loaded into nano-carriers can deliver in a controlled and sustainable manner the drug in the vicinity of the bacteria that cause TB (Swai, 2012; Dube et al., 2013; Chang et al., 2015).

The technique of manufacturing the nanoparticle anti–TB drug is novel and it was successfully patented in the USA under patent number US 8-518-450 (Kalombo, 2013). The patent which was granted on 27 August 2013 under the name "Nanoparticle Carriers for Drug Administration and Process for Producing Same" is described as follows:

> *The invention provides a process for the production of nanoparticle carriers for drug delivery, said nanoparticles being produced by preparing a double emulsion of water-oil-water including one or more polymer which forms the basis of the nanoparticle carrier, blending the drug to be delivered into one of the emulsion phases, doping either the oil-phase or the outer-water phase with a carbohydrate, and spray drying the emulsion to form nanoparticles of a narrow particle size distribution of 10 nm to 100 nm, which nanoparticles are substantially spherical.*

Through the exploitation of the patent, the researchers encapsulated conventional anti-TB drugs namely isoniazid, rifampicin, ethambutol and pyrazinamide into a single drug.

Theoretical Framework

In order to assess the considerations that are made in balancing the potential risks and benefits associated with the drug, the study is anchored in the Social Construction of Technology (SCOT) theoretical framework. SCOT argues that human action is influential in shaping technology. It asserts that the ways in which a technology is developed and subsequently used can be explained by understanding how it is embedded in its social context (Pinch and Bijker, 1987). SCOT provides a foundation for analysing societal factors in the development of a technology. As originally presented by Pinch and Bijker (1984), SCOT's conceptual framework is characterised by inclusion of relevant social groups, and by interpretive flexibility, stabilisation and closure.

In this study, the focus is on two of these concepts, namely relevant social groups and interpretive flexibility. The relevant social groups are the starting point for the analysis using the SCOT approach. The concept of relevant social group denotes institutions and organisations as well as organised and unorganised groups of individuals. The key requirement is that all the members of a group share the same set of meanings attached to a specific artifact (Pinch & Bijker, 1984; Bijker, 1995). In this way, the relevant social groups are the embodiments of particular interpretations of a technology. The concept of interpretive flexibility suggests that technological artifacts possess different meanings for various groups (Pinch & Bijker, 1984). It implies that the development of a technology is an open process capable of producing different outcomes depending on the social circumstances (Pinch & Bijker, 1987; Bijker, 2006). The interactions within and among relevant social groups give rise to different meanings of the technology (Bijker, 2006). In this study, the concept of interpretive flexibility is used to show how the assessment of potential risks and benefits differs from one group to another. Stabilisation and closure refer to a state when problems with the use of a technology disappear

(Pinch & Bijker, 1984). The latter takes place over time, when the interpretative flexibility collapses through closure mechanisms. In the development of a technology, there are controversies that arise due to different interpretations, which lead to conflicting images of an artifact. As a result, the technology continues to undergo modifications until such conflicts are resolved and no longer pose problems to any relevant social group. When a technology reaches closure and stabilisation, no further modifications occur and it fortifies in its final form.

As the drug was still under development, the study deliberately does not apply the concept of closure and stabilisation because the drug was not yet embedded in society. By using the SCOT, the development of the drug is treated as a political process involving multiple groups, each embodying a specific interpretation of the technology.

Methodology

Data were collected by means of semi-structured interviews with stakeholders. A total of twenty stakeholders, namely the producers of the technology, patients, nurses, and care givers, were purposively selected in relation to the objectives of the study. The inclusion of different stakeholders rendered the study a multi-site ethnography, which according to Marcus (1998) does not simply mean extending one field site to multiple field sites, but reconstructing the connections between different sites. The interviews were conducted in English and they ranged from 30 to 60 minutes. To facilitate data analysis, the interviews were recorded with consent from the respondents and transcribed. Atlas.ti software was used to analyse the data, by assigning code labels which were grouped into larger themes for analysis. The coding of the data was meant to annotate findings, weigh and evaluate their importance and assess the relationships between them.

Assessment of Potential Risks and Benefits of the Drug

Stakeholder Groups

In assessing the considerations that are made in balancing potential risks and benefits, relevant social groups were engaged in the study. These are the developers of the technology, patients, caregivers, nurses and a doctor. Table 1 provides a summary of the stakeholders who participated in the study.

Table 1. Summary of stakeholders who participated in the study

Type of Stakeholder	**Number of Stakeholders**
Developers of the drug	5
Patients	6
Nurses	4
Caregivers	5
Doctors	1
Total	**21**

As shown in Table 1, the study is not exhaustive of all the stakeholders. For example, medical doctors are the key stakeholders who did not participate in the study, as it was difficult to schedule interviews with them due to their work commitments. As a result, only one doctor was interviewed; as one respondent fell short of the requirements for a relevant social group, the interview was not included in the analysis.

The Developers of the Drug

In the eyes of the developers of the nanoparticle anti-tuberculosis drug, it was a breakthrough technology in the treatment of TB, a disease that has caused a lot of suffering to South Africans. The developers viewed it as a lifesaving drug that would positively change the treatment and control of TB. According to one of the researchers in the project:

> *Nanotechnology for drug delivery offers a suitable means of delivering drugs to the target. This means that the drug goes exactly where it is supposed to work. There is no overdose and wastage, which means it is effective. With the intake of the drug being reduced to once a week, there is a high chance of compliance from the patients so it works in that way.*

From the statement above, the researcher valued the ability of the nanoparticle anti-tuberculosis drug to address the problems caused by conventional anti-tuberculosis drugs. The new drug was considered to be superior to the conventional TB medicine. In this context, the new drug came as a lifesaver in the sense that it ensured that the patients complied with the treatment, thereby enhancing the chances of curing the disease. The researcher raised challenges in the use of the conventional drugs, but did not talk specifically about the potential risks associated with the use of nanoparticles in the drug. What is explicit from the views of this particular researcher is that the assessment of the drug was done in the context of the prevailing problems in the treatment of TB. Reference was made to the conventional treatment of TB which has existed for close to half a century, but failed to control the disease. Based

on this assessment, the conventional drugs were a failure in the eyes of the research group, hence the nanoparticle anti-tuberculosis drug was regarded as a viable alternative. This was revealed in a statement by another researcher in the project who argued that:

> *The biggest problem with the current therapeutic regimen for TB is that the drugs should be taken once a day for a period of six to nine months in order to be effective. Also, according to the World Health Organization (WHO) Direct Observed Treatment short course programme, the drugs need to be taken in the presence of a healthcare practitioner. To improve patient compliance with TB treatment, we are developing a way that will ensure that the antibiotic drugs are released and taken up in the affected cells over a longer period using nanoparticles.*

The researcher emphasised the benefits of the new drug in relation to conventional drugs. She mentioned the problems of the conventional medicine and the solutions that were provided by the new drug. In terms of side effects, she focused on how the new drug reduced the negative impacts caused by conventional anti-tuberculosis drugs and did not discuss the potential risks associated with the nanoparticle anti-tuberculosis drug in particular. Another researcher in the project responded to a question on what he considered important in the development of the new drug by making the following remarks:

> *The potential and promising clinical applications and the associated social and economic benefits of nano enabled anti-tuberculosis drugs provide an incredible enticement to roll out the drug to the market. As we develop the drug, we take into consideration that TB is a poor man's disease, which means it is not a popular choice for development by commercially driven pharmaceutical companies.*

By referring to the poor, the researcher interpreted the benefits of the drug in terms of targeting the vulnerable people in society, whose challenges in most cases are not given attention. The researchers were not only preoccupied with exploiting the benefits of the drug, but also considered the potential risks, particularly those related to toxicity. According to a researcher in the project, they were aware of the controversies surrounding nanotechnology in terms of potential side effects. As a result of this, they were pro-active in that they sought the services of experts on the toxicity of nanomaterials. This was done by collaborating with partners who assisted in assessing the potential risks, as indicated in an interview:

> *As a research group, we explore the side effects of the drug. For example, we have been assessing the toxicity of the drugs when administered in mice and in that area, we work with various stakeholders. Through in-vivo animal experiments and ex-vivo laboratory tests, we understand the interaction of nanobodies in the body and take corrective steps. We cannot rule out the possibility of side effects, but at the moment there are no known risks that can stop us from developing the drug.*

The researchers considered the risks of using nanoparticles as a matter of concern. They were guided by best practices meant to minimise the risks of nanoparticles.

The Patients

The TB patients had their own way of interpreting the potential risks and benefits of nanoparticle anti-tuberculosis drug. Their assessment of the drug was based on their first-hand experience with conventional anti-tuberculosis drugs. They pointed out that conventional drugs were burdensome as indicated by a patient who was bedridden at a hospital in Johannesburg:

> *Being under medication for six months is not a joke. It is a painful process that one has to endure. And after six months it is not guaranteed that you are cured, you can develop a multi-drug resistant strain which needs more medication. With regard to the drug that you are talking about, I would take it without hesitation. I do not mind the side effects which you said are not yet proven. Look at the pimples that I have developed, my body smells [of] drugs, it is horrible to say the least.*

Due to the challenges which the patients experienced in the treatment of tuberculosis, the nanoparticle anti-tuberculosis drug was viewed as a better substitute as they had lost hope in the conventional anti-tuberculosis drugs. The patients chronicled their challenges with conventional anti-tuberculosis drugs, indicating that staying in the hospital was boring, but going home was even worse. Some of the patients indicated that due to poor health, they had lost their jobs and exhausted their savings while seeking treatment. Against such a background, the patients welcomed the nanoparticle anti-tuberculosis drug as a medication that would reduce their suffering. The patients were less bothered by the potential risks of the drug, which they overlooked due to their experiences with conventional anti-tuberculosis drugs. A TB patient indicated that the benefits of the new drug outweighed the potential risks by arguing that:

> *I have nothing to lose by trying and using the new drug. Instead, it gives me hope and I might benefit from it. If the drug you are talking about reduces the period of treatment, that is good news for me and I am sure my colleagues too. You see, I have been in the hospital for three months and I am told that I still have several months to go. I miss my family, but I would not opt to go home today if given a choice because the drugs that I take need a lot of food and I am not be able to fend for myself when taking the drug.*

Some of the TB patients indicated that they were prepared to face the risks as long as they enjoyed the benefits that came with the drug. It emerged that when people are desperately focused on survival, the form in which the solution arrives and its effects tend not to matter much.

The Nurses

The nurses had their own interpretation of the drug. As the health practitioners who interact directly with the patients, the nurses knew the challenges of the conventional drugs. As some patients opted to skip taking the drugs, which is the major cause of multi-drug resistance, the nurses bore the burden of persuading the patients to take the drugs to ensure compliance to the treatment. A senior nurse in the TB control unit pointed out that:

> *Working in the TB ward is one of the worst experiences that I had here. The conventional drugs are too much such that spending months taking the same drugs needs a lot of persuasion. When the patients do not take the drugs accordingly, the disease is not cured. To see a patient dying because he/she could not follow the treatment is really sad. Sometimes, I end up blaming myself for failure to convince the patients to take the drugs as per the prescriptions, but it is a difficult process. At the end of the day, we ask ourselves are we safe in the wards with tuberculosis. The exposure that we have in the wards is risky for our health.*

The nurses were concerned about the risks of contracting the disease from TB patients coming for treatment. The TB wards are usually congested, therefore the chances of contracting the disease are high. The nurses expressed a preference for the use of the nanoparticle anti-tuberculosis drug as it would bring the benefit of treating the patients in a relatively short period of time. In addition, compliance to the treatment because of patients taking a single drug per week would probably make it easier not to admit TB patients unless they were critically ill. That would lead to reduced workload for the nurses and also result in less contact with TB patients. Another nurse pointed out that he sympathised with TB patients as the conventional treatment is cumbersome. However, as a nurse he was obliged to ensure that patients comply with the treatment.

To the nurses, the process of giving drugs to patients when they know that there are low chances of compliance is demotivating. Based on their previous encounters with TB patients, the nurses viewed the nanoparticle anti-tuberculosis drug as a better alternative to the conventional drugs. The nurses focused on the benefits of the nanoparticle anti-tuberculosis drug and paid little attention to the unknown risks of the nanoparticles.

The Caregivers

The tuberculosis patients who are discharged from hospitals are cared for by home-based caregivers. In some cases, TB patients are discharged when they are still critically ill and in need of further management at home. This occurs despite family members not having the necessary knowledge and skills to care for the critically ill patients. The caregivers consist mainly of relatives of the patient, such as spouses, children and parents. The duties of TB caregivers involve managing medications, bathing the patient, and taking care of household chores, meals and bills. The caregivers form the interface between the patient and the medical practitioners. In the execution of their duties, the caregivers face challenges in providing food and attending to hygiene needs. Financial constraints as well as psychological and physical exhaustion increase their burden. The caregivers supervise and monitor the patient's levels of activity and ensure that scheduled appointments with health care providers are met. These duties exert pressure on family members caring for the TB patients at home. Given such a background, the considerations by the caregivers in balancing the potential risks and benefits of nanoparticle anti-tuberculosis drug were influenced by the circumstances in which they found themselves as they cared for the TB patients. In an interview, a father who was caring for his son argued that:

> *I already feel tired of caring for my son who is ill. It is now the first month and I still have five months to go and as I told you, my duties start early in the morning... as I prepare warm water for the patient to wash his body. I then prepare food as he cannot take the drugs on an empty stomach otherwise he will feel dizzy. After that, I go and fend for the family as I am the breadwinner. Therefore, the drug that you are talking about is most welcome, it will help ease my burden.*

Providing care for TB patients is highly demanding and it interferes with the daily work of the caregivers. The burden of taking care of TB patients also involves providing a clean environment. Such an environment is important to enable the patient to recover and stop the spread of the disease in the family. A mother who was caring for her son revealed that:

> *When my son was discharged from the hospital, he had not fully recovered. In fact, he was weak and got tired easily. He could not do anything by himself and since he had no wife, I took the responsibility of washing his clothes and tidying his room. The room where he sleeps needs to be cleaned thoroughly. At times, he spoils his blankets. I think he is reacting to the medicine which he takes every day. However, the most difficult task was when he started refusing to take the drug saying it was causing side effects.*

The caregivers who were interviewed revealed the challenges that they faced as a result of taking a cocktail of conventional anti-tuberculosis drugs. Despite the challenges, they had no choice other than continuing being supportive to give hope of survival to the patients and avoid being judged negatively by society. Thus, the caregivers interpreted the new drug as a potential solution that would relieve them of their daily burden.

Discussion

The considerations that were made by different stakeholders in balancing potential risks and benefits revealed the interpretive flexibility of the drug, in that various social groups attached different meanings to the drug.

The developers assessed the drug based on its technical properties in ensuring targeted delivery. This was in sharp contrast with the patients, nurses and caregivers who assessed the drug based on their lived experiences. They focused much attention on the benefits of the drug, particularly the shorter treatment time and lower dosage and attached more weight to what the drug meant in the context of their day-to-day life. Their considerations were based on the social context from which they defined what constituted potential risks and benefits of the drug. The meanings of the drug went beyond what the developers considered in the laboratory. What was remarkable about the considerations of these social groups was that they did not limit their interpretation of the drug based on what the drug could do, but also considered the impacts it had on society and individuals. The social groups defined the problems of TB differently and as a result the solutions that were brought by the drug were defined differently. In this way, the interpretive flexibility of the drug was made explicit.

The interpretive flexibility as portrayed in this paper indicates that technologies are sufficiently underdetermined to allow for multiple interpretations. As the drug was culturally constructed and interpreted, there was flexibility in how the stakeholders interpreted the technology and this was mainly a function of vested interests. This confirms that the deployment of technologies in society is a multi-faceted process in which diverse social groups, cultural values and local practices are implicated. Thus, it is not enough to define a technology's success or failure by focusing only on functionality, but it is important to consider the landscape of all the stakeholders and how the technology is nested in its broader social, political and cultural environment, which influence how potential risks and benefits are assessed.

Previous studies on the assessment of potential risks and benefits of nanotechnologies have focused primarily on developed countries and the discourse is focused on democratic risk governance (Macnaghten, et al., 2005; Barben et al., 2008;Van Asselt & Renn, 2011) rather than the influence of the context in which the technologies are used. The findings of the study have implications for the development of new technologies, particularly in developing countries, where the relevant stakeholder groups may have different perspectives on risks and benefits to those of their developed-country counterparts.

Conclusion

The case study has highlighted that the lived experiences of different social groups influence the considerations that are made in balancing potential risks and benefits of technologies. The literature on nanotechnology often focuses on the risks associated with the technical properties of nanoparticles, which were also the concern of the scientists in this study. However, the results show that as soon as the technology is set in a specific context, other considerations start to matter too and these may be indirect and not linked to the technology. Particularly, patients, nurses and caregivers were influenced by the challenges they encountered in the treatment of tuberculosis.

Thus, the assessment of a technology is not complete without considering the social conditions that surround it, in addition to its technological aspects. A better understanding of the mutual dependence of technologies and society at different levels of policy is important in understanding how potential risks and benefits are balanced. The assessment of a technology prior to its distribution in the physical form is a pro-active approach meant to solicit stakeholders' concerns and values and this is done more effectively when the technology is not yet entrenched in society. This enables an iterative development process that considers the perspectives of the different user groups. It transforms the assessment of the technology from being the domain for experts to an all-encompassing process involving laypeople. This in turn shifts the analysis of the technology from being technological to sociological.

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