INTRODUCTION
1. INTRODUCTION

The shift from the industrial to the modern age brought with it many benefits for humans, such as reduced poverty and improved health and longevity; but along with this has come a great many hazards. As observed by Ulrick Beck, modernization has become ‘its own theme’ as the ‘questions of the development and employment of technologies are being eclipsed by questions of the political and economic ‘management’ of the risks of actual or potentially utilized technologies’[1]. The discourse on risk has heretofore been the purview of scientific experts who define the risk agenda based on the probability of the physical harm resulting from technological processes. However, the march towards an ever-advancing modernity and the widespread distribution of associated harms has forced a new dialogue on risk. The global impact of hazards in the modern age (e.g., increased cardiovascular disease resulting from an approved MS drug impacts patients in all countries where the drug is approved and used; harm, in the industrial age, is no longer local) has exploded the one-dimensional probabilistic view, and risk is now considered to be inclusive of not only the probability of the harm but also the consequences of the harm.

Modernization has forced this movement of risk beyond the confines of the laboratory, and sociologists, anthropologists and scientists now acknowledge the new risk paradigm; however, the risk paradigm implies the introduction of a degree of subjectivity heretofore unacknowledged in the modern technological discussion. This belated refinement of the experts’ view on risk emerged at the moment it became apparent that the public were not accepting of the scientists’ explanations of the harms resulting from new technologies (e.g. nuclear energy, herbicides) and was also the impetus for an additional didactic on risk—that of the ‘public perception’ of risk [2, 3]. The field of risk research flourished with the efforts to explain and contain the public’s allergic reaction to the results of this new modernity with countless publications providing theories of the layperson’s divergence from a normative approach to risk (expected utility) [4, 5]. We now know that people perceive risk via a number of cognitive biases, subjective interpretations of the hazard/harm, affective reactions and individual differences, such as gender [5-8].

Ironically, the new paradigm on risk did not result in greater inclusion of laypeople or non-experts in the dialogue on risk, as their subjectivity was still seen as a drawback and not as support of equitable policies. Instead, a now discredited knowledge-deficit model was developed with the purpose of enlightening an ignorant and hostile public [9, 10]. Challenges to this model since the 1990s have supported a shift from deficit to dialogue, seeking to link science to the body politic. The aspiration for democracy in science is aptly summed by Moore, who says that ‘technical is political, the political should be democratic
and the democratic should be participatory’[11]. However, in the past two decades, several criticisms of the actualization of this aspiration have been raised[12]. Barnett and others have recently argued that ‘the construction and expert control of public concern invites interactions framed in terms of expert reassurance rather than mutual exchange and engagement’ [13]. Beck, Wynne and others have refined the concept of ‘dialogue’ and argued for the need for reflexivity of scientific institutions, that is, institutions where the science–public interface is inclusive of the non-expert concerns and where the resulting policies bear out the continual negotiation that non-experts are forced to exhibit between the benefits and risks of developments in science [1, 14]. The play between experts and non-experts in other areas of science is similarly enacted within the realm of medicine. In Europe and the US, the institutions that assess the scientific advances in medicine and regulate the associated risks endeavour to engage the public by including representatives of patient organisations [15-17]. While laudable, this construction is reminiscent of the ‘knowledge-deficit’ model rather than the ‘dialogue’ model and, as with other such engagements, ‘seems to do little more than replicate existing power relationships between scientists and the public’[12, 18]. In a recent look back at public engagement in science, Patrick Sturgis questions whether this use of the ‘scientific citizen’, an institutionally sponsored self-selected representative of the public, fulfils the commitment to public engagement [19]. Sturgis’ essay raises a dilemma; if a single representative is insufficient and the more democratic approach, that is that all members of the public engaged in face-to-face discourse with scientists, is an impossibility, how can social scientists deliver on the promise of normative commitment to public engagement?

The continuance of the knowledge-deficit model of public–scientific interaction, despite its newer forms, results from the near infallibility of expert knowledge. While the public were undergoing scrutiny for their cognitive limitations, biases and inability to understand/accept the associated risks of the advances of science, social scientists neglected to conduct a similar examination of the ‘expert’ group. Here, a distinction must be made; by ‘expert’ I refer to not only those with scientific knowledge but also to those who are the gatekeepers for the advances in technology and science and who operate within organizations and institutions to manage and control the risk and therefore define the risk agenda. Stemming from the methodology used in the early studies of risk and the main thrust of the research, that is, explaining the public ‘technophobia’, experts were viewed as assessing risk only via a function of probability and consequence, while laypeople have a more complex and socially charged view of risk. This view has now been sufficiently criticized, leaving it with limited if any credibility [20]. However, despite the criticisms of Rowe, Wright and others, new studies among ‘experts’ have not lead to a greatly improved understanding of how experts interact with risky situations and whether the social construction of risk,
cognitive biases in judgment or the influence of emotion and individual characteristics operate among experts in the same or similar manner as among non-experts.

- In *The Tolerability of Risk*, Ortwin Renn summarizes the work of Webler (1995) and Demos (2004) and proposes the following dimensions to ensure the equitable and balanced assessment of risk:
  - Have all arguments been properly treated? Have all truth claims been fairly and accurately tested against commonly agreed standards of validation?
  - Has all the relevant evidence, in accordance with the actual state-of-the-art knowledge, been collected and processed?
  - Was systematic, experiential and practical knowledge and expertise adequately included and processed?
  - Were all interests and values considered, and was there a major effort to come up with fair and balanced solutions?
  - Were all normative judgements made explicit and thoroughly explained? Were normative statements derived from accepted ethical principles or legally prescribed norms?
  - Were all efforts undertaken to preserve plurality of lifestyles and individual freedom and to restrict the realm of collectively binding decisions to those areas in which binding rules and norms are essential and necessary to produce the wanted outcome?

Do experts, particularly those who work in regulatory institutions, adhere to these steps? On the surface, it would seem that they do. There are elaborate processes in place within our regulatory organizations to support adherence to the above generally agreed principles [21], and there is a pervasive belief that such decision making bodies by virtue of their organizational structure, that is, by relying on a hierarchal bottom-up flow of expert advice and consultation, allow for alternative interests and perspectives to be rationally considered until the optimal alternative is reached [22]. However, there is evidence to contradict this view. That is, real-life organizational decision making, despite the procedural support provided, is prone to both cognitive and organizational limitations and the problems of ambiguity, uncertainty, conflict and differing risk attitudes that may negatively impact the elucidation and consideration of the alternatives [22]. One obvious reason for the limitations to the very logical process described above is that institutions are managed or composed of individuals who, despite their best efforts to the contrary, may influence the outcome by the introduction of ‘human factors’ into the decision-making process.

1.1. Research Scope and Aims

It is the human aspect of risk regulation for experts and non-experts that will be examined in this thesis using methods from the fields of behavioural economics and decision
theory. The overarching research questions are whether and how decision making for risk regulation, as conducted by experts within the European pharmaceutical regulatory network (a decentralized system for regulation and consensus building for medicinal products and devices across 28 European countries), is influenced by known behavioural and cognitive limitations. In addition, we must ask if there is an existing method(s) that responds to the challenge of moving public engagement on risk assessment out of the procedural (e.g., limited engagement of a small number of representatives working within the current evaluative structure) and into the political (i.e., interaction with the public that is reflective of their concerns and of their humanity. Two well-known theories will guide this section of the work—the psychometric paradigm and decision theory. Further, two decision tools (qualitative and quantitative) will be evaluated for their ability to increase transparency and to support the regulatory decision-making process.

The chapters that follow will provide support for the case of ‘risk as a social construct’ among medically trained experts but not, as has been previously proposed, a construction based on characteristics of the ‘risk’ but based on individual differences in risk perceptions and risk attitudes. I will argue that like laypeople, experts as regulators have a subjective component to their risk assessment of medicinal products that is a combination of a heuristic or ‘gut feeling’ reaction depending on the situational factors surrounding the medicinal product, their general attitude towards risk and their individual characteristics. This thesis aims to answer the following questions via several empirical studies:

- Are there benefits or risk dimensions of a drug that predict the risk perception of an assessor? (Chapter 2.1; accepted, *Medical Decision Making*, March 2013)
- Do medical assessors have a consistent risk attitude, that is, risk-seeking, risk-neutral or risk-averse? (Chapter 2.2; accepted, *Value in Health*, January 2015)
- Is there a relationship between risk perception of a drug and individual characteristics such as personality traits or general risk attitude of an assessor? (Chapter 2.2; accepted, *Value in Health*, January 2015)
- Do medical assessors exhibit congruency in their views of the benefits and risks of a drug? (Chapter 2.3; submitted for publication)
- Can multi-criterion decision support tools aid regulators in the decision-making process? (Chapter 3.1; accepted *Drug Discovery Today: Technologies*, March 2011)
- Is there an existing methodology that can be applied to the elicitation of patient preferences? (Chapter 4.1; submitted for publication)
- Are the risk attitudes and treatment choices different between MS patients and regulators? (Chapter 4.2; submitted for publication)
2. CONCEPTUAL FRAMEWORK

The interdisciplinary nature (medicines, risk regulation, behavioural economics and decision theory) and therefore complex structure of this thesis requires the elucidation of several concepts that underpin the work. First is the conceptualisation of risk and how it is operationalised within the context of drug regulation; second is a combined concept of affective responses and human cognitive biases when faced with uncertainty and third is the influence of individual differences in risk assessment and choice.

2.1. Risk

In the past four decades, developments in science, medicine, and technology have led to increasing public concern that the promised benefits bring with them serious potential harm to the environment and to human health. In the area of pharmaceutical regulation, there are two situations that reflect this concern: when regulators withhold market approval of new medicines despite lengthy pre-clinical and clinical evaluations and when high-profile medicinal products are first approved and then later withdrawn from the market. The debates before and after both instances highlight the diversity in risk attitude, that is, a chosen response to a situation among experts, patients and other stakeholders in that they did not all share the same views on risk [23].

The case of Natalizumab (Tysabri) provides an excellent example of all the concepts related to risk assessment to be outlined in this thesis. Approved by the US regulator in 2004 as a treatment for multiple sclerosis, it was withdrawn in 2005 by the manufacturer due to three cases of a rare and fatal neurological condition, progressive multifocal leukoencephalopathy (PML). With no new cases occurring, the FDA returned Tysabri to the market in 2006 after a review of the safety data and intense lobbying by patient organizations. The EMA, on the other hand, did not provide market authorization after receiving the application in 2004 but deliberated the evidence for two years before finally approving Tysabri with a limited indication in 2006. By 2012, there were 212 known cases of PML, but to date the drug has not been withdrawn from the market again [24]. Here, we see the probability of a harmful event, a socially determined response to this probability and differences in risk attitudes among various social groups. The situation above begs the question: if three fatalities were too many, how can 212 fatalities now be acceptable? I submit that the answer to this can best be found among the empirical studies of risk research.

2.1.1. Risk as Uncertainty

From the above example of Tysabri, we see that individuals have differences regarding the degree of risk they are willing to accept. But what is risk? How is it defined? The
definition most often applied in scientific enquiries is that risk is a measurable, objective function of the probability of an event and the magnitude of that event [25-27]. But even this definition does not sufficiently cover the full complexity of what comprises risk. Within the context of medicinal drugs, it appears that regulators must contend with both risk and uncertainty. Prior to placing a drug on the market, uncertainty dominates as manufacturers conduct clinical trials to support their bid for market authorization. However, there are limitations attached to the knowledge gained in clinical trials that is inherent to the methodology, namely the comparatively narrow patient populations on which the drugs are tested, the continual supervision of the patients during the trial period (neither of which are reflective of a real life setting) and the limitations of the statistical models used to assess such data.

The table below shows an attempt by Wynne to untangle the intricacies of risk and uncertainty.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Known odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty</td>
<td>Don’t know the odds: may know the main parameters, may reduce uncertainty but increase ignorance</td>
</tr>
<tr>
<td>Ignorance</td>
<td>Don’t know what we don’t know; ignorance increases with increased commitments based on current knowledge</td>
</tr>
<tr>
<td>Indeterminacy</td>
<td>Causal chains or networks remain open</td>
</tr>
</tbody>
</table>


Given the definitions above, the assessment of all clinical trials, including the case of Tysabri, appear to reflect uncertainty and not risk because the true probability of adverse events cannot be known at the time of market authorization and may in fact be higher in the target patient population than was observed in the clinical trials. The relevance of this concept for this thesis is that medical assessors are on the verge of assessing a quantity that is not entirely measurable. In the context of the traditional definition of risk first given in this section, if the true probability of an event is unknown then one cannot determine the magnitude or the consequence of such an event. There must therefore be some other system by which assessors judge the viability of medicinal drugs.

2.1.2. **Risk as a Social Construct**

An alternative view of risk proposed by social scientists is that risk is not an objective entity (probability and magnitude) but a social construction [29-32]. There are two main
theories of risk as a socially constructed concept, only one of which is the focus of this thesis and for which the background literature with the main findings and gaps in the knowledge are presented below. The other, known as cultural theory, has too wide a focus for this thesis and was found to be difficult to evaluate within our research population. This theory, as proposed by Mary Douglas and Aaron Wildavsky, holds that humans understand or perceive risk via culturally supported value systems or worldviews [33]. Four worldviews have been proposed: egalitarian, individualist, hierarchist and fatalist. The empirical evidence in support of this theory has been limited, and to date, the theory has been strongly criticized. However, new data from a series of experiments from the Cultural Cognition Project has shown that this is a viable area of study and is deserving of further attention [34].

2.1.2.1. Risk Perception

In the field of risk research, the seminal work by Starr showed that the acceptance of risk was not, as previously thought, based only on weighting the objective estimates of risks and benefits but also included a subjective dimension that he identified as voluntariness, meaning that people are willing to accept greater risks associated with voluntary activities (e.g. driving) than with involuntary activities (e.g. consuming food preservatives [35]. There have been many challenges to this work, but it began an exploration of the subjective component in the construction of risk and launched a new era of research.

In the 1970s, the work of Fischoff and others and later Slovic and others further expanded this theme of the subjective component in risk evaluation. They concluded that while the objective component of a hazard, an agent that leads to harmful consequences, remains real (e.g. birth defects in families living near nuclear plants or the number of automobile accidents on the highway), people make subjective decisions with regard to how dangerous they perceive these hazards to be. The authors also concluded that there are specific characteristics of a hazard that influence risk acceptability [2, 25, 36]. Based on the now famous analysis of the perception of 54 hazards collected by laypeople, the graph of how people ‘perceive’ risks, that is, via three dimensions (third dimension not shown on graph) of dread—the unknown, the number of people exposed to the hazard and one’s own exposure—was published and the term ‘risk perception’ was coined. This theory, known as the psychometric paradigm, set the stage for all other discourse on the understanding of risk.

From the above discussion, one gathers that there are two radically different paths by which experts and laypeople view risk, the traditional definition and the social construction of risk. If one considers the case of Tysabri, the above definitions appear to be operational but curiously in contrast to what has been previously proposed. One could construe that
the experts (i.e. the manufacturers/regulators) in their decision to withdraw the drug from the market after three fatalities used the social definition of risk, that is, dread of future deaths from PML, a rare but fatal disease, while the patients instead may have used the traditional definition by recognizing that the probability of PML was low, although the consequence, death if the disease occurred, cannot be considered minimal. It appears that this division of the views on risk, by virtue of this example, seems artificial and, as noted by Mary Douglas, is perhaps too simple a construction. Instead, she merges the two views and proposes a definition that encompasses everyone (laypeople, experts) and emphasizes another aspect of risk evaluation, that is, value. ‘Risk is not only the probability of an event but also the probable magnitude of its outcome and everything depends on the value that is set on the outcome. The evaluation is a political, aesthetic and moral matter’ [37].

2.1.2.2. Risk Attitude

It is very often said that western societies have become ‘risk-averse’, and consequently, the governing bodies have developed regulations aimed at protecting the public from any risk [38]. The label of being ‘conservative and risk-averse’ is often directed at drug regulators when a drug application is rejected or withdrawn from the market [39, 40]. Indeed, regulatory bodies within the EU have as a statutory requirement to operate within the context of the precautionary principle that covers cases ‘where [the] scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level
of protection chosen by the EU’ [41]. Consequently, there are known regional differences that occur between the experts. From 1995 to 2010, of a sample of 325 medicinal products (non-generic) approved by the FDA, four applications received a negative opinion by the EMA and 46 applications were withdrawn prior to opinion. Conversely, of the 504 products approved by the EMA from 1995 to 2010, seven had a ‘not approved’ status from the FDA at the time of the EMA opinion. One could say that patients in Europe were either protected from the risks or denied the benefits of the drug compared to the patients in the US, depending on one’s viewpoint. Further inconsistencies are seen within the European Regulatory Network. Between 1998 and 2011, there were 60 applications where regulators reviewing the same data arrived at divergent views [42].

It remains a challenge for regulators to balance increased public demand for long-term health, longevity and social acceptance (e.g. obesity) with the scientific uncertainty attending drug development and their ethical responsibility that requires that they err on the side of caution when the harm is scientifically plausible but uncertain. The answer to whether medical assessors/regulators in Europe are risk-averse with regard to drug regulation may be determined by evaluating individual assessors’ attitudes towards risk in general life situations and the relationship, if any, to their benefit or risk judgment of a drug.

2.1.3. Cognitive Judgment and Affect

The work of Kahneman and Tversky on the inconsistencies and contradiction of human behaviour to established economic theory, expected utility (EU), spanned a 30-year period. During this time, they published the results of several experiments of human choices leading to the following conclusions:

- emotion always overrides logic in the decision-making process;
- people suffer from cognitive dysfunction in making decisions because they never have enough information;
- people are not risk-averse but rather are loss-averse [5]

The final point above reflects an important alternative to EU, Prospect Theory (PT), and proposes that when making decisions under risk, people are more sensitive or place greater value on losses than on gains. Individuals evaluate choice outcomes relative to a reference point and are willing to take more risks in choices involving sure losses and take less risk in choices involving sure gains, relative to the reference point [5]. In our health-related example of Tysabri, we see that PT could be used anecdotally to explain the choice of the patients, that is, when faced with a sure loss of a chronic debilitating disease if they did not take the drug, they were willing to take the risk by lobbying to keep the drug on the market despite the threat of developing PML. While plausible,
there is limited empirical investigation for the relevance of PT to patient choice, and researchers have called for more investigation of its applicability to decisions in the health domain [43, 44].

2.1.4. Individual differences in risk perception, risk taking
The literature examining individual difference yields several findings that are relevant to the hypotheses of this thesis; that is, humans do not all perceive risks or act in the same way when faced with uncertain situations. In their meta-analysis of 150 studies on gender differences in risk taking, Brynes et al have supported a longstanding belief of differences in risk taking between males and females. However, the major contribution of this work is the finding that these differences are not constant but change over time, with men taking fewer risks at older ages, resulting in a smaller difference between men and women [45]. This change of risk taking over time is supported by a recent study by Rolison et al, who show that not only does risk taking change but that the differences may depend on the domain being examined [46]. The authors found that the mean rating for financial risk taking, as measured by the Domain-Specific Risk-Taking (DOSPERT) scale, decreased sharply in later life, more so for men than for women. Meanwhile, risk taking in the social domain decreased more sharply for women than for men. Recreational risk taking had greater decreases between the younger and middle years than in later life, and ethical and health risk taking decreased linearly. As with many studies in risk perception and risk taking, the population providing the data have mainly been non-expert, non-professional populations. However, a few studies have been carried among managers and those with similar professional training, and the differences between genders are considerably less than in non-professional populations [47-50]. This finding is of particular interest as regards this thesis, as one hypothesis is that even within an expert population gender may influence risk perception and risk taking. The research mentioned above has been carried out predominantly among professionals/managers within the financial domain and may not be extrapolated to all expert domains. The literature indicates that individual differences in the perception of risk and consequently risk taking may be influenced not only by gender, age and domain but also by a general feeling of security or rather insecurity, education and socio-economic status [51, 52], that is, those who feel they are on the outer fringes of society are more risk-averse than those who feel content with their place in society, have a degree and earn a substantial income.

There is clear evidence that individuals approach risky situations differently, and there are some discernible trends with regards to perceiving or taking risks. Explanations offered for the differences noted indicate a far more nuanced evaluation of risk than
was proposed by early work in this area. A seemingly clear dichotomy such as gender has now been challenged, and other descriptors such as age, social-economic status, professional grouping and cultural conceptions of masculinity and femininity have begun to emerge.

**THESIS OUTLINE**

The first three chapters of this thesis present the results of field studies aimed at evaluating the psychometric paradigm among experts conducting risk evaluation within the pharmaceutical regulatory environment. Two of these chapters have been published and one has been submitted for peer review. The fourth chapter, already published, provides results of decision support tools being evaluated within the pharmaceutical regulatory environment and shows that it is feasible to integrate such methods within the existing benefit-risk evaluation process. The two final chapters present an advance on the previous chapter by using a multi-criteria approach to capture preferences for treatment outcomes among patients and among experts (medical assessors) for ‘real’ decisions, both of which have been submitted for peer review. From this we can begin to quantify where the expert and the non-expert values on acceptable benefits and risks differ and where they converge. New paths for communication between all stakeholders in the field of medical research can be forged and the concepts of *dialogue* and shared decision-making realised within the field of pharmaceutical regulation.
REFERENCES


MEASURING RISK PERCEPTION