Science of Uncertainty: Making Cases for Drug Incorporation in Brazil

Alex Gertner
Princeton University

Abstract
Public health efforts around the globe are increasingly dominated by concerns over access to high-cost medicines. These drugs bring new benefits and potential risks to bear on populations and greatly impact government budgets and priorities. This article explores how scientific evidence is being mobilized to inform decisions concerning the incorporation of health technologies in Brazil. I conducted interviews with experts and observed the work of a start-up company based in Rio de Janeiro that performs economic analyses on behalf of the pharmaceutical industry. These analyses are used by the Ministry of Health to decide whether or not to incorporate new technologies.

The article shows that, in performing economic analyses, company employees sought to locate/construct from known/measured parameters, a need/demand for the drug within the public system, thus creating a market. Uncertainty is not merely an incidental obstacle of the company’s work but a core feature of its practice. The strategic use of uncertainty allows for the dis-
placement of public health priorities by commercial interests and the supplanting of what is sensibly sound by what is methodologically permissible.

[Keywords: pharmaceuticals, health economics, evidence-making, uncertainty, Brazil]

“This health technology assessment is a new wave,” Anderson Pereira, an official at the Brazilian Ministry of Health, told me in one of a row of uniform public buildings in the planned city of Brasilia in August of 2008. At the time, Pereira, a doctor, was responsible for making recommendations to the Minister on health technology incorporation decisions, that is, which drugs and medical devices would be used within Brazil’s public healthcare system. In 2006, the Ministry of Health had overhauled the institutions responsible for the incorporation of new health technologies. In the new incorporation system, the Ministry opened itself to proposals for new technologies. These proposals consisted primarily of economic analyses, and, as in earlier policy (re)formulations, the “rational use” of drugs was heavily implicated in the reform rationale (see Guimarães 2004).

Pereira was in charge of the newly-formed commission that analyzed proposals and made recommendations to the Minister. A Ministry paper outlining the reform stated, “The unsystematic incorporation and use of inadequate technologies create risks for users and compromise the health system’s overall effectiveness” (Decit 2006). Pereira made it clear he had no illusions about the incorporation system’s limitations. He confirmed that most proposals were for new high-cost drugs for genetic disorders affecting small numbers of patients and that, though the commission was open to proposals from any source, nearly all of them came from the drug industry. The Ministry lacked professionals to adequately assess proposals and had yet to make the incorporation scheme transparent, Pereira said.

In contrast to the Ministry’s neatly stated goals of systemization, Pereira saw a complex system encompassing both public and private fields of practice wherein various actors were struggling to identify their interests and how best to pursue them. “Brazilian society builds things and then thinks about how to fix them,” he said, “it changes the wheel of the car while the car is driving.”
Global Pharmaceuticals and Evidence Production

Public health efforts around the globe are increasingly dominated by concerns over the development, access, and distribution of pharmaceutical products (Petryna et al. 2006; Biehl 2006, 2007a, 2007b; Farmer 2001; Ecks 2008; Whitmarsh 2008; Geest et al. 1996). Anthropologists Adriana Petryna and Arthur Kleinman propose the notion of a “pharmaceutical nexus” to capture and examine the “broad set of political and social transitions that fall under and to some extent happen through the globalization of pharmaceuticals” (Petryna and Kleinman 2006:21). The pharmaceutical nexus is useful precisely for its ability to bring into view the varied fields of practice and theory that are altered through the creation and distribution of pharmaceutical remedies. Petryna’s work in the globalizing of pharmaceutical clinical trials demonstrates how fields of evidence use and production are also at stake in these “political and social transitions.” Globalized commercial interests, variable ethical notions, and national public health priorities can be elaborated through evidence-producing practices (Petryna 2006, 2009).

Evidence concerning public health efforts and interventions is gaining in importance as governments are struggling with how to best guarantee sustained access to healthcare for their populations. With increased pressure to justify decisions and maximize resources in public health, the practice of basing decisions on evidence, rather than relying directly on other bases for policy, such as societal input or commercial interests, has been gaining popularity (Niessen 2000:859). Economic evidence, in particular, has been increasingly used, especially in the United Kingdom, Canada, and Australia and especially for health technology incorporation decisions (Drummond 2001).

In Brazil, anthropologist João Biehl, who coined the expression pharmaceuticalization of public health (2007a), writes on how the creation of the AIDS program depended, in part, on the government’s ability to generate economic forms of evidence that justified the program’s costs to its transnational sponsor, the World Bank, and its ability to contest pharmaceutical knowledge-monopolies in drug price negotiations (Serra 2004, Biehl 2007b). Even so, health officials disregarded Biehl’s own attempt to generate evidence concerning the program’s systematic exclusion of certain social groups (Biehl 2007b:218-223). As Biehl’s work shows, through the contestation and implementation of particular notions of evidence, health efforts are legitimized or compromised, populations are deemed worthy of treatment or systematically disregarded, and markets either expand or are left unexplored.
With the pharmaceutical nexus and the recent history of the Brazilian AIDS program in mind, we cannot responsibly understand the development and use of economic evidence for technology incorporation in Brazil as a self-evident application of scientific principles or a rational evolution of decision-making practices, as implied in the Ministry’s reform rationale. Rather, as Pereira’s comment suggests, we must be suspicious of tidy constructions and sensitive to areas of uncertainty. We must consider the use of economic evidence in incorporation decisions as responsive to localized public and private demands and implicated in global pharmaceutical politics.

**Health Net: Making Models, Making Markets**

At about the same time as the Ministry of Health was introducing the new system for health technology incorporation, two long-time friends in Rio de Janeiro, a professor of medicine in a public university and an owner of a group of private clinics, decided to start a health technology assessment (HTA) company that I will call Health Net. HTA has developed as a way to assess the effectiveness, safety, and cost of technologies in order to inform health and policy decisions. HTA has many definitions (Goodman 2004), but as a set of practices it includes various forms of evidence creation, analysis, and review.

Health Net’s first project was to conduct an economic analysis of an anti-cancer drug with the purpose of requesting its incorporation into the *Sistema Único de Saúde* (SUS), Brazil’s public healthcare system. Monica Barros was the first engineer Health Net hired. “I was frantic,” Barros said jokingly, “People took everything I said as an absolute truth.” Health Net now specializes in preparing the economic analyses the Ministry requires for the incorporation of new technologies, and Barros is the company’s most experienced engineer. Health Net typically executes these analyses on behalf of the companies that own the technologies, mostly drugs. By late 2008, Health Net was the only company of its kind in Brazil and had grown from the two founders and Barros to a full-time staff of three doctors, a nurse, four engineers, a secretary, and a chief financial officer. Its clients included local subsidiaries of seven of the ten largest drug companies in the world ranked by revenue at the time (MedAdNews 2007).

From mid-June to August of 2008, I conducted participant-observation and semi-structured interviews in Health Net. The company provided a
place from which to view reforming government policies, emerging market strategies, and evolving scientific practices. The creation of health technology assessments at Health Net typically involved negotiating evidentiary, methodological, and ethical ambiguity in the presence of clearly-defined commercial interests and nebulous notions of the public good. Even as Health Net employees struggled to identify the Ministry’s expectations, to satisfy drug company’s demands, to meet transnational methodological standards, and to negotiate a set of self-imposed ethics, the company thrived. Uncertainty was not a recurrent obstacle in their work; it was the norm. This article explores the sources and types of uncertainty that emerge within a “rational, evidence-based” system for health technology incorporation and how company employees responded to it.

To understand the sources and types of uncertainty involved in Health Net’s work, one must understand some of its particulars. The particular type of HTA Health Net conducts can be categorized as technology-oriented assessments, “intended to determine the characteristics or impacts of particular technologies,” especially the economic and public health impacts of mass technology use or implementation (Goodman 2008:16). In conducting such technology-oriented assessments, this company employed almost exclusively integrative methods, used to synthesize and analyze existing evidence taken from published studies and reports, rather than primary data methods, used to collect original data. Central to Health Net’s practice was the production of mathematical models. Modeling is “used to answer ‘What if?’ questions.” In other words, it is “used to represent (or simulate) health care processes or decisions and their impacts under condition of uncertainty, such as in the absence of actual data or when it is not possible to collect data on all potential conditions, decisions, and outcomes” (Goodman 2006:45). The construction of a model allowed employees to then perform an economic analysis of the results, typically either a cost-effectiveness analysis or a cost-benefit analysis.1 Such analyses were always used to compare two or more treatments in order to demonstrate one’s superiority.

The daily work of Health Net employees revolved around the creation of these mathematical models and economic analyses, from the collection of evidence for the models, to negotiation with the model’s sponsor on its particular goals and parameters, to presentation of results. These models and analyses were meant to simulate how a particular technology would behave within SUS, the public healthcare system: what it would cost, what
benefits it would have, what forms of treatment it would ease or replace, and so on. For a model to be reliable, its input parameters, such as the drug’s effectiveness and how many patients would receive it, must be well-measured or accurately estimated, and the relationships between parameters must be well-understood and represented within the model. No model is perfect, and models may be subjected to uncertainty analyses to attempt to determine their reliability. Indeed, all evidence-production involves uncertainty, and I do not intend to discredit HTA by revealing it to be no different from other fields in this respect. Rather, my aim is to identify sources of uncertainty and offer a critical understanding of responses to it. In order to illustrate some of the challenges involved in producing analyses, I will begin by describing the case of a particular drug. The remainder of the article will discuss how these challenges stem from areas of incomplete or uncertain knowledge and practice, implicated in global pharmaceutical politics, and how Health Net’s employees managed these uncertainties.

The Case of Rivex

When I arrived in mid-June of 2008, Health Net was finalizing an economic analysis for a drug company of the impact of including a new drug in SUS, Brazil’s public healthcare system. The pharmaceutical company wished to incorporate the drug into the country’s list of “essential medicines,” which would necessitate its widespread availability. The drug, which I will call Rivex, was intended to treat a significant cause of child and infant mortality in Brazil. I sat in on the presentation Health Net’s analysts made to the drug company representatives.

Health Net’s analysts found through a systematic review of literature that Rivex could reduce hospitalization time for children with severe cases of the disease from 5 to 3 days on average, but there was no evidence in published literature that it reduced mortality. In other words, the drug would not affect the disease’s contribution to child and infant mortality in the country. Even so, as long as the cost of Rivex was less than the cost of a 3 day hospitalization, one might suppose that the drug could still reduce costs for SUS. This cost-saving potential could in itself be a rationale for incorporation. Indeed, the drug was relatively cheap, but, according to the analysts, this argument did not hold because of the way the drug would be financed. SUS creates resource packages for patients being
hospitalized according to different conditions or diagnoses. According to a diagnosis, the hospital releases a certain amount of money from SUS for treatment.\textsuperscript{3} As long as the child survives, SUS is not concerned with how the hospital uses the resource package, the analysts said. So if a new drug has no effect on mortality, SUS has little incentive to change existing directives in order to incorporate it.\textsuperscript{4, 5}

There was another problem, the analysts pointed out, as the disease in question presents with rather generic symptoms, and doctors in this context are not in the habit of testing for a particular diagnosis before beginning what could be beneficial treatments. Rather, patients in SUS might receive a generic diagnosis, such as “fever” or “diarrhea” and be given the drug just in case. As a result, more children than have the disease would likely receive the drug as a precaution, though how many more would depend on the prescriptive habits of doctors, making an accurate economic analysis of the drug’s use difficult. Unconvinced that the drug was suited for the list of essential medicines, the analysts proposed that the pharmaceutical company market it privately outside of SUS.

If it decided to carry through with its incorporation proposal, the pharmaceutical company that owned Rivex would be asking the government to pay 25 million dollars over 5 years for the drug. This figure was based on the prevalence of disease in 2005. However, one of the pharmaceutical company’s employees noted that in 2006 a vaccine for the disease began being implemented in some populations. Since then, no assessment of the incidence or prevalence of this disease had taken place. As a result, the analysts had to revise the model according to estimates of prevalence and incidence based on the scope of vaccination and the effectiveness of the vaccine. Since less of the drug would be necessary, this revision would likely reduce the total cost. The pharmaceutical company employees, who had frequently interrupted the presentation with questions and criticisms, were relieved by this. They believed a lower amount would increase the chances of the drug being incorporated. Over lunch, the Health Net analysts complained about the pressure drug companies put on them to produce favorable analyses. They noted that failure to have a drug incorporated could cause the drug company staff to lose their jobs.

As I explained above, a mathematical model is constructed from several known or, rather, measured parameters. In the case of Rivex, these parameters included the drug’s effect, the population’s epidemiological profile, physicians’ prescriptive habits, and the health system’s financing
mechanisms. Knowledge of parameters is inevitably incomplete. The incidence and prevalence of disease are estimates, prescriptive habits are unknown, and the health system’s financing mechanisms are not always properly understood. Even the effect of the drug can be highly uncertain. Frequently, drug companies demanded models and analyses be reconfigured if they did not present favorable results. Health Net employees struggled with the nature of the evidence they used for models, the rigor of their methods, and the ethical dimensions of their work.

Uncertain Evidence: Quality and Context
In discussing the challenges of their work, company employees consistently cited the dearth of available information or evidence for the construction of models. In particular, they were frustrated by the lack of public health data specific to Brazilian populations and treatment contexts. Simple public health data concerning disease prevalence were frequently incomplete or out-dated, as in the case of Rivex. A discussion of the limitations of data reporting, aggregation, and analysis by the Ministry of Health is beyond the scope of this study. However, many Health Net employees, having worked in SUS, were sensitive to the unreliability of reported data at the source. Sandra Marchi, a nurse, was responsible for conducting systematic literature reviews and assisting with constructing mathematical models. Sometimes the needed data existed in health posts, she said, but it was “written by hand, mixed with other papers, in some notebook, inside an old cupboard, and no one knows where it is.” When aggregated data was available, it was through difficult-to-navigate online databases.

Employees said data concerning the effect of interventions on Brazilian populations was also lacking. The employees presumed the typical Brazilian patient would likely respond differently to a medical intervention than, say, a European or North American patient because of differences in diet, environments, genes, etc. They attributed the dearth of Brazilian studies to the absence of a “research culture” among Brazilian health professionals, though certainly the availability of funds to properly study every relevant intervention and the nature of global clinical research were also contributing factors (Petryna 2006, 2009). In the absence of national public health information, company employees frequently used foreign sources of data. During my time at Health Net, employees were working on a model for a device I will call Endomaz to
treat menorrhagia, heavy menstrual bleeding. Marchi, who was assigned
to the project, was using data on the efficacy of Endomaz and the patient
satisfaction associated with its use from a randomized clinical trial con-
ducted in the United Kingdom. “I have to assume the data is similar [for
Brazil], but it’s obvious that it isn’t,” she said.

When it comes to HTA, notions and standards of rigor are typically
concerned with the “quality” of evidence used to conduct integrative
studies such as economic analyses, and not with the context in which the
evidence is produced. Quality is typically judged by studies’ design,
which demonstrates a concern for studies’ internal validity (Rychetnik
2002:121). Evidence hierarchies explicitly rank the quality of evidence
according to the design of the study that produced the evidence
(Rychetnik 2002:121). Randomized controlled trials (RCTs) are considered
uniquely able to avoid biases associated with other study formats and, as
a result, are considered the gold-standard in primary data collection
studies. RCTs are nonetheless also subject to biases, and must be carefully
planned and carried out in order to effectively avoid them. Many RCTs
are funded by drug companies, and there has been much concern over
the reliability of these (Damdron 1986, Easterbrook 1991, Smith 2005,
Heres et al. 2006). According to reigning notions of evidence quality,
Marchi was entirely justified in utilizing the British RCT data. The
Ministry of Health’s health technology incorporation submission form
even has an evidence hierarchy table printed on it. She knew, neverthe-
less, that the “quality” category alone was insufficient to fully assess the
reliability and understand the implications of evidence utilized for pub-
lic health decision-making.

Dobrow et al. (2004) argue that it is insufficient to consider only the
“quality” of the evidence as determined by study design in public health
decision-making. The contexts in which evidence is produced must be
considered. Contextual factors can be taken into account through evalu-
ative categories such as “relevance, appropriateness, applicability, accept-
ability, and utility” (Dobrow et al. 2004:214). The authors remind us that
technologies necessitate their own context-specific considerations and
practices, requiring knowledge from care-givers and accommodations
from patients in implementation. Implicated in the authors’ arguments is
a concern for the relevance of evidence collected in one epidemiological,
institutional, and clinical setting to other dissimilar settings. Such “con-
text-specific” forms of knowledge and assessment challenge the seeming
universal applicability of “high-quality” evidence but are, nevertheless, excluded from evidence hierarchies.

Indeed, RCTs are purposefully intended not to produce context-specific data. Rather, RCTs are intended to produce measures of efficacy, the capacity of a treatment to produce an effect. These are different from measures of effectiveness, the actual effects of a technology once it is implemented in real-life care environments where mistakes take place, resource constraints may disrupt therapy, and patients with multiple disorders may not respond as well to treatment—that is, the very nature of efficacy trials requires them to be conducted in highly controlled circumstances with selective populations. As a result, RCTs may not even be representative of the regional contexts in which they are conducted. “Controlled conditions” used for efficacy trials should not be taken for granted, and, as anthropologist Andrew Lakoff discusses in the case of anti-depressants, demonstrating favorable results can depend upon selecting the “right patients” for the trial (2002).

In such highly-controlled trials, real-life uncertainties, such as those discussed in the case of Rivex, are not present. These trials are both highly context-specific, because they occur in highly controlled conditions, and wholly non-specific, because they supposedly produce a measure of a drug’s theoretical ability to work. According to Petryna (2009), pharmaceutical companies make the non-specificity of evidence produced through trials into an advantage. Clinical trials of products intended for developed-country markets are increasingly conducted in developing countries. Because results are not region-specific, they can be extended to virtually any locality. The non-specificity of clinical trial results follows from a biomedical understanding of treatment that favors measures of efficacy over effectiveness. Lakoff (2002) writes that in the biomedical understanding of treatment “the drug is understood to operate directly on a physical problem through its biochemical effects on the body of the patient” (73). This understanding leaves no room for the influence of contextual factors on treatment success. Because a drug’s effectiveness is virtually assured to be less than its efficacy, the application of evidence on efficacy to HTA models results in optimistic results for the drug’s marketers. Recently, there have been calls for more “pragmatic” randomized clinical trials that enroll varied patient populations and may be carried out within existing healthcare infrastructures (see Tunis et al. 2003, Treweek and Zwarenstein 2009).
To sum up, in the absence of Brazilian data concerning public health measures and clinical outcomes, employees relied on data from foreign sources bolstered by general notions of evidence admissibility based on study design. Such notions of evidence admissibility stem from a narrowly-conceived biomedical understanding of treatment and are implicated in the global commerce of evidence production. As Marchi’s comment makes clear, however, these accepted notions offend the obvious. Where guidelines or consensuses on evidence admissibility are tenuous or inexistent, standards of evidence can be molded to meet local interests and needs, while preserving the semblance of rigor. In such cases, what is methodologically permissible may disagree with what is sensibly sound.

Marchi, who had worked in public health posts and private clinics, suspected many of her patients would prefer Endomaz over a hysterectomy, the standard treatment in SUS, but no such data was available. Rather, she had evidence concerning patient satisfaction with treatment from other countries. As Marchi’s comment demonstrated, in the absence of categories and practices to assess sensible concerns, configurations that favor commercial interests are free to take hold. The tools (language) to critique such approaches or include other-dimensional concerns in analyses either do not exist or, as Dobrow et al. note, are not considered as part of evidence hierarchies. When employees did try to include “on-the-ground” perspectives from the public healthcare system, it was typically through panels of doctors. Since such panels rank very low on evidence hierarchies, employees avoided this option whenever possible.

The suggestion here is not that company employees altered their evidence standards according to immediate commercial interests nor that they were insensitive to the importance of local contexts. Company employees simply relied on generally accepted norms concerning evidence “quality” from existing scientific literature, having no reason or incentive to do otherwise. Where areas of knowledge uncertainty or analytical absence are bolstered by commercial interests, rigorousness loses traction, and logical considerations, such as feasibility and patient preferences, are easily elided.

**Uncertain Methods: Harmonization and Pragmatism**

Despite the uncertainties they detected in the evidence they utilized, Health Net employees needed to find ways to rigorously assess the technology in
question and present it in a favorable light. While the previous discussion has focused on uncertainties associated with evidence, employees also had to deal with complex and subjective comparison criteria and results from models. Such challenges bring to light methodological uncertainties in the employees’ practice. When it came to the Endomaz project, the studies for various alternative treatments did not utilize the same efficacy measures or follow-up periods, making comparison within a model difficult. The use of dissimilar measures between trials can be a strategy used by clinical researchers to manipulate the outcome of studies and constituted another challenge in Health Net employees’ work. In a review of head-to-head trials of second-generation anti-psychotics, for instance, Here’s et al found that trials testing the same drugs frequently came to opposite conclusions (Heres et al. 2006). In 90.0% of studies, the outcome was in favor of the trial’s sponsor. The authors identified dosing, entry criteria, and reporting of results as only some sources of bias (Heres et al. 2006).

“[Endomaz] is better than the other ones in parameters that have no appeal,” Marchi said. In other parameters, Endomaz was at times better but not within statistical significance. Endomaz was less efficacious than a hysterectomy, the standard treatment in SUS for menorrhagia, and had lower satisfaction ratings in the literature. On the other hand, it was also less expensive and produced fewer complications than a hysterectomy.

Employees needed to reduce these complex trade-offs to an un-ambiguous argument in favor of one intervention. They considered inventing their own measure of effectiveness, “cost per satisfied patient,” in order to demonstrate/construct Endomaz’s superiority. Just as uncertainties pervaded the use and selection of evidence, they were present in the construction of models and economic analyses.

“When we look back, there is always something that could have been done better,” Barros, Health Net’s most experienced engineer, said. Like the other engineers, Barros had not had any experience performing economic analyses of health technologies before working for Health Net. “No one studies this in college, not production engineers, not economists, not statisticians, not doctors, not nurses, no one,” Marchi said. While employees had found a correspondence program on the economic evaluation of health technologies from a British university, they knew of no comparable programs in the Brazilian educational system. Even so, nearly every employee was engaged in a graduate program or some other form of continuing education while working at Health Net. Through conferences and
congresses, conversations and partnerships with other researchers, reading articles, and, ultimately, this long-distance program at a British university, Barros gained a working-knowledge of HTA practices that coalesced into a form of expertise.

According to Marchi, the pharmaceutical industry employees she worked with frequently did not understand the methods used to conduct economic analyses. “Most people who do pharma-economics in the industry don’t understand the step-by-step processes involved in these analyses. They understand the general concepts,” she said. “They sometimes ask questions that someone who doesn’t know anything about the field would ask.” In this atmosphere of uncertainty, the creation of economic analyses involved frequent consultation with pharmaceutical companies and reconfiguration of parameters until a model could be reached that produced some sort of favorable result for the technology in question. “In reality, the client frequently doesn’t know what he wants,” Barros said referring to the different types of models and analyses that can be performed and to the drug company employees who commission them. But they know they want to request incorporation, I asked. “Yes, that they know.” She continued, “They know, for example, that they want to solicit the drug’s incorporation into the list of exceptional drugs…but they don’t know how they will do it or if it can be done. How can one ask for the incorporation of a drug that doesn’t demonstrate benefits? Impossible.” Even so, Barros recognized that the demonstration of benefits can be subjective as in the case of Rivex described above.

Indeed, the demonstration of benefits may be highly dependent on which two treatments are being compared. A treatment may look favorable in comparison to one alternative but not another. Fernanda Amaral, a psychiatrist who performed systematic literature reviews at Health Net, confirmed that pharmaceutical representatives frequently do not know what kind of analysis they need, and analysts can go through several configurations before reaching a satisfactory result. “They want to compare [the drug] to something that will show a good result,” she said. “You can decide on something and at the end, when they see the result, they may decide they don’t like it and want to change everything.” Amaral said employees tried to make the case to pharmaceutical companies that it was the “drug which isn’t good, not the analysis.” As in Lakoff’s (2002) work with clinical trials, the drug is the stable reference point and all other variables are alterable.
The Ministry of Health does formally require that technologies being proposed for incorporation be compared in economic analyses to best existing treatment. Presumably, the Ministry issues this guideline in order to maintain equal standards across technologies and to minimize subjectivity in analyses—a technology is either better than the current best or it is not. Nonetheless, this sort of analysis does not always take place. “Many of our treatments lines are so technologically defunct that the comparisons are not against the gold-standard but the treatment used in SUS,” said Pereira, the Ministry of Health official responsible for making recommendations to the Minister.

High-income countries with experience utilizing HTA to inform policy decisions, such as the United Kingdom and Australia, have lengthy and detailed guidelines on the use and application of economic analyses in technology appraisal (NICE 2007, PBS 2008). In Brazil, where few have experience or knowledge of HTA, the Ministry’s guidelines offer little more than general suggestions on what kinds of studies should accompany proposals, saying nothing about how these studies should be conducted, according to what standards or best set of practices (Ministério de Saúde 2006). According to the manager of an international member-based organization of agencies and individuals involved in health-technology assessment, HTA is an “emerging discipline” even in North America. Efforts to fully “harmonize” HTA practices have only begun in last 2 years, he said, and have primarily taken place in Europe (see Hutton et al. 2008). He confirmed that the harmonization of HTA practices is particularly difficult in developing countries that have typically had little experience with the field.

Harmonization efforts may offer a way to address current issues in HTA such as how to treat the context-specificity of evidence. In a recent article on the history and future possibilities of harmonization of evidence admissibility in HTA, Hutton et al. write, “…Whereas some aspects of economic evaluation remain highly context-specific, there is scope for further exploration of harmonization of others” (Hutton et al. 2008:513). They suggest standards for evidence admissibility given divergent contexts may be different across indications, but they stop short of offering any suggestions on what standards should be or how to determine them, indicating harmonization may be a far-off goal. Even if some form of harmonization were achieved it would not necessarily result in common standards for evidence admissibility. As Petryna (2006) discusses in the field of clinical trials, “the ethical standard for the world was claimed to be vari-
ability” in part through the International Conference on Harmonization (44). In other words, harmonization can be used to institutionalize uncertainty and promote local variability in settings where commercial interests dominate research practices and prerogatives.

Even as Health Net employees sought to learn about and emulate European and North American HTA practices, they responded to localized needs and priorities. One study employees were particularly excited about sought to make a case for the incorporation of an expensive medication to treat a rare genetic disorder. Andre Silva, a professor of medicine and one of Health Net’s founders, explained that it is difficult to make a case for treatments for rare conditions where there is no existing alternative treatment for comparison. He decided Health Net would compare the cost-benefit relationship for Brazil’s AIDS program with a program to be created for this rare disease. The implied question was, “if the government will spend a certain amount on an AIDS patient, why not on another type of patient?”

“Brazil’s AIDS program is its vitrine to the world,” Silva told me. The Portuguese word vitrine can be translated to mean “display-case,” though its most frequent meaning is “shop-window.” The commercial connotation is apt, considering Brazil’s growth as a drug market, the AIDS program’s increasing budget for antitroviral drugs, approximately 227 million dollars in 2005 (Grangeiro et al. 2006), and the program’s origin in an administration that championed neo-liberal reforms (Biehl 2007b). In this project, Health Net employees utilized trans-national methods and appealed to local sensibilities to produce an argument of effectiveness as well as equality. Standardization and innovation occurred together, producing a study that was a sort of patchwork of trans-national authorizing practices and a locally-appealing rationale.

The significance of harmonization for HTA, a relatively young field, extends beyond ethical or methodological flexibilities, however. The shop-window metaphor is not merely one of cold, calculating, commercial opportunity. As neo-liberal reform rationales employ arguments concerning “opening-up to the world,” Silva’s shop-window metaphor communicates a longing, for approval, purchase, acceptance. Science historians Steven Shapin and Simon Schaffer (1985) recount how Robert Boyle developed various strategies or “technologies” to extend the “empirical experience” in 17th century England. “The role of Boyle’s literary technology was to create an experimental community, to bound its discourse internally and externally,
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and to provide the forms and conventions of social relations within it” (Shapin and Schaffer 1985:77). The significance of harmonization for the scientific integrity of HTA may be fully appreciated in light of this statement. Harmonization is best understood not as a standardization of methodologies but as the bounding of a self-legitimizing transnational community. It is not only important for the methodology to be public, but for it to conform to a bounded set of methodological allowances. Company employees relied on various sources of methods because of their own inexperience, as a kind of self-regulation, but also because they searched for the creation of such a community and for inclusion in it. In such communities, members can agree on what forms of uncertainty are legitimate and what forms are not. Uncertainty is not so much eliminated as some forms are slated for elaboration and others excluded. Employees could at times crave standardization even as they took advantage of opportunities resulting from its absence.

Marchi considered not carrying on with the analysis for Endomaz given the apparent methodological impossibility, but later she said she “found a path.” Such paths were paved with various forms of evidence, and their shapes and directions were defined by methodological allowances, commercial interests, existing evidence, and notions of what serves the public good, partially conceived through the Ministry of Health’s supposed expectations. Methodological allowances were stable but sufficiently flexible to allow for several possible configurations of analyses. Commercial interests largely determined the ultimate form these analyses took. As in the case of Rivex, analysts also attempted to preempt what the Ministry of Health would find favorable in a drug. Where within the health system a technology was proposed for incorporation depended on which properties of the technology were demonstrated, which depended both on which could be demonstrated and which Health Net had an interest in demonstrating. As the Rivex case shows, which properties could be demonstrated depended on existing evidence, funding mechanisms within the public system, clinical forms of common sense, and how the technology’s benefits interact with the existing healthcare system.

Ultimately, in making models and conducting economic analyses, Health Net’s members sought to locate/construct from known/measured parameters, a need/demand for the drug within the public system, thus creating a market. Psychiatrist David Healy (2006) writes, “The portfolio of marketing maneuvers has grown…Clinical trials and ghostwritten scientific articles have increasingly become part of the marketing of disorders
and their treatments... The result is a growth of disorders tailor-made to fit ever more visible drugs” (62). According to Healy, pharmaceutical companies’ (re)construction of disorders to fit existing pharmaceutical arsenals involves altering/manipulating the nature of disorders. In Health Net’s work, the context of drug delivery, the health system itself as well as the alternative treatments available, is (re)constructed in mathematical models and within methodological allowances until it favorably fits the characteristics of proposed drugs.

Bruno Latour contends that the laboratory’s ability to make knowledge claims that are of interest to members of society arises from its potential to translate the field in the laboratory and the laboratory in the field. “…The laboratory positions itself precisely so as to reproduce inside its walls an event that seems to be happening only outside—the first move—and then to extend outside to all farms what seem to be happening only inside laboratories” (Latour 1983:266). A model is not the healthcare system, but the translation of the healthcare system. The power of Health Net analysts lies in their ability to convincingly recreate the healthcare system.

However, one cannot extend laboratory before extending “the conditions of verification that existed in the laboratory” (Latour 1983:272). Indeed, efforts seem to be underway on the part of the Ministry to improve data production and management throughout SUS. A May 2009 Ministry decree stated, “Information is fundamental for the democratization of Health and the improvement of its management. The computerization of the activities of the Sistema Único de Saúde (SUS), within the appropriate protocols, is essential in order to decentralize health activities and make viable Social Control over the utilization of available resources” (Ministério de Saúde 2009). As I stated earlier, Health Net employees were sensitive to the unreliability of reported data at the source. Amaral stated that doctors in her psychiatric hospital would misreport what treatments patients received in order to provide them with newer drugs while receiving reimbursement from SUS. Computerization of health activities will likely not address the principal reasons and ways in which health professionals misreport information. Even as the rules of the laboratory are extended into new fields, we must be sensitive to how these rules represent opportunities rather than simply restrictions.

According to Latour, certainty is created in the laboratory through the ability to make mistakes. “Certainty does not increase in a laboratory because people in it are more honest, more rigorous, or more ‘falsifica-
tionist.’ It is simply that they can make as many mistakes as they wish…Each mistake is in turn achieved, saved, recorded, and made easily readable again, whatever the specific field or topic may be” (271). In light of Latour’s statement, Health Net’s practice of reconfiguring models until a rationale for incorporation emerged becomes less sinister and more mundane. Latour does not pretend these certainties are not guided or selected according to interests. Indeed, he credits Pasteur’s success in part to his ability to “capture” the interests of farmers (259-260). However, to say interests are necessarily involved in experimentation is not to say that which interests in particular dominate is irrelevant.

Pereira, the Ministry of Health official mentioned earlier, noted that at some point commercial interests meet public needs. “After all, [pharmaceutical companies] are not producing astronautical artifacts, they are producing health products.” As economist Michael Kremer discusses, however, pharmaceutical drug development is overwhelmingly directed towards developed world diseases, rather than developing world health priorities (Kremer 2002). The confluence of technology incorporation and public health priorities becomes in practice a chance occurrence.

In his work on the effect of pharmaceutical representatives on prescriptive patterns in Argentina, Lakoff (2006) writes, “…The mutual imbrication of science, regulation, and business in the circulation of pharmaceuticals is best seen not as a contamination of pure science but rather as part of a distinctive and emergent regime for authorizing knowledge claims and expert action” (112). Similarly, the production of models involved not a distortion of methods by interests, but the construction of an “authorized knowledge claim.” Authorized methods, such as the use of evidence hierarchies, learned from various authorized sources, such as the British university, were used to construct such claims. Ultimately, Health Net’s methods were successful for their ability to satisfy commercial interests while making use of scientific knowledge-making technologies.

**Uncertain Ethics: Rigor and Interests**

To say the final forms of the economic analyses Health Net performed were largely defined by commercial interests is not to say the employees were somehow sold to the pharmaceutical industry. In fact, the employees frequently viewed the industry with suspicion and distaste. “I wouldn’t want to work in the industry,” Marchi said. She and other employees
had turned down job offers to work for pharmaceutical companies at increased pay. In justifying these decisions, employees cited the openness and flexibility of their current positions. These preferences overlapped with ethical concerns as well. “If I work for the industry, I have to swear to the ends of the Earth that [the product] is marvelous,” Marchi said, regardless of what she thought or what the evidence may suggest. Health Net employees mentioned that failure to have a technology incorporated could lead to pharmaceutical industry employees’ termination.

Health Net employees openly discussed their opinions of the technologies they assessed. When it came to Rivex, the engineer responsible for the project plainly told me, “[Rivex] is bad.” Despite their efforts to construct favorable analyses, employees said it was clear when drugs were “good” or “bad” and trusted that Ministry officials would be able to make decisions accordingly. Employees gathered to laugh and sneer at a presentation Rivex’s sponsor planned to show the Ministry of Health. The presentation contained cartoon slides telling the story of a young girl falling ill after being contaminated during play with her friends and taking Rivex to get better (see Martin 2007 for imbuing drugs with personalities).

Employees greatly valued working for drugs they thought were good. “When you have projects where you believe in the drug, it’s very good,” said Amaral, who had worked in a public psychiatric hospital before coming to Health Net. In the hospital, studies comparing treatment were of little worth, she said, since most drugs were in shortage and many patients ended up receiving haloperidol, an older anti-psychotic with serious adverse effects, in the place of newer treatments. “Your distance to the patient is very great but so is your responsibility to him,” Amaral said of her HTA work. In the absence of formal ethical guidelines, employees relied heavily on their own sensibilities.

Working in favor of pharmaceutical interests they did not always trust, and marketing products they frequently did not approve of, employees were highly conscious of questions of ethics and responsibility. “You’re not selling a bed-sheet where the worst that can happen is that it is a lousy bed-sheet and no one dies as a result,” Marchi said. “The ethics are in the methods. It is clear for all to see,” Silva told me, encapsulating the view held by many in Health Net. As a professor in a public university, Silva performed economic analyses directly for the Ministry of Health with the help of one or two of Health Net employees who were also his graduate students. At the time, he was performing in his academic role an analy-
sis Health Net had performed for a pharmaceutical industry client. Silva said that ideally he should not be permitted to perform the analysis. However, he added, “Conflicts of interest are only problematic when people are unethical.” He noted it was in Health Net’s long-term financial interest to maintain a rigorous methodological ethic.

The manager of the member-based HTA organization proposed a similar viewpoint, “If you go deep enough in any relationship you’ll find a conflict of interest. The issue is how do you deal with it? Do you recognize it and manage it, in which case everyone benefits…or do you pretend it doesn’t exist in which case it comes back to bite you later.” As long as Health Net did not compromise itself methodologically, Amaral argued, it was always serving the public good, either by demonstrating a technology was good or demonstrating it was not. In these configurations, ethics are dislodged to either methods or interests, and do not seem to exist as a separate field to be considered on its own terms.

Despite these conceptions, ethical ambiguities still arose in Health Net’s business practices. Employees struggled with how to set up a contract with clients, given that mid-way through a project they may come to the conclusion that a favorable economic analysis was simply not methodologically possible. They resisted the suggestion that a favorable analysis could be produced for every product. Nevertheless, employees said they had only produced one analysis that showed a decidedly negative result for a client. Even so, completed analyses were delivered to pharmaceutical companies, which held the right to alter them, before going to the Ministry of Health. The Ministry of Health has not made health technology incorporation decisions, much less the economic analyses that supposedly inform them, public. As a result, neither is it possible to independently assess the quality of such analyses nor to determine to what extent the Minister relies on such analyses to inform incorporation decisions.

Final Considerations: Cultivating Uncertainty
While a discussion of the origins of the importance of rationality and economic evidence in public health is beyond the scope of this study, some important trends and milestones can be identified. Since the mid-1990s Canada, Australia, and European countries, particularly the United Kingdom, have been giving greater importance to economic evidence in
public health decision-making, particularly in health technology incorporation (Drummond 2001). At about that same time, the World Bank’s *World Development Report 1993: Investing in Health* proposed cultivating economic development as a means of improving health, recommended redirecting government spending to “more cost-effective programs,” and utilized disability-adjusted life years (DALYs) to quantify disease burden (World Bank 1993).

In addition, as Biehl’s work shows, the World Bank’s support of Brazil’s universal antiretroviral policy depended on the program’s ability to generate economic forms of evidence that justified its costs (2007b). Biehl also explores how the AIDS program arose in the midst neo-liberal state reforms (2007b). At first glance, then, the rationale for the Ministry of Health’s new system of health technology incorporation seems rooted in novel forms of economic governance arising in certain developed democracies, elaborated through a then-growing transnational force in global health, and consistent with neo-liberal forms of thinking that served to justify the universal antiretroviral policy, regarded internationally as an enormous public health success.

When I spoke to Pereira, the Ministry of Health official, in August of 2008, he indicated the Ministry would be making its incorporation decisions public beginning in November. Since then, another institutional restructuring has taken place, he is no longer involved with technology incorporation, and the incorporation decisions are still not made public. The Ministry’s failing is not that it did not succeed in constructing a rational system of incorporation or that it does not account for commercial influence, but that it has not allowed for a public discussion of the merits and limitations of its approach. Shapin and Schaffer (1985) write, “We regard our scientific knowledge as open and accessible in principle, but the public does not understand it…A form of knowledge that is the most open in principle has become the most closed in practice. To entertain these doubts about our science is to question the constitution of our society. It is no wonder that scientific knowledge is so difficult to hold up to scrutiny” (343). Rationality was a given in the Ministry’s justification for reform. As shown, in practice, evidence production and interpretation are highly subjective and necessitate managing several forms of uncertainty.

HTA is positioned as a way of allowing governments to make “rational decisions” or, put differently, to ensure resources are used “rationally.” Its ability to appear neutral is derived both from the use of scientific “trap-
“pings” and knowledge-making technologies, but also its success in satisfying all of the immediate commercial demands and public expectations placed upon it. As in other “audit cultures,” the efficiency and costs of intermediary processes are well-managed, while ultimate measures of effectiveness are overlooked (McDonald 2000:64 and see Strathern 2000). Health Net employees worked to produce high-quality analyses and Pereira claimed to scrutinize these as rigorously as possible. In the meantime, little consideration was given to attracting technologies that responded to public health priorities or to monitoring the ultimate effect of technologies once implemented.

In all, strategies to manage uncertainty involved eliding problematic forms of knowledge, relying on commercial interests to evaluate analyses’ configurations, and relocating ethics to more familiar fields of practice. These strategies reveal an extreme discomfort with uncertainty, and accounting for uncertainty often involved attempting to minimize it in ways that veiled, disqualified, or dislodged it. Actors were frequently unable or unwilling to communicate their concerns. Marchi, the nurse, knew of the limitation of her use of British evidence but had no immediate way, reason, or incentive to address it. Silva wondered about the ethics of his work but lacked a critical framework or accountability mechanisms with which to scrutinize it. And Pereira recognized crippling limitations of the health technology incorporation system, but saw no timely ways of addressing them. Petryna notes how the practical uncertainties involved in global clinical trials are obfuscated in their final presentations (2009). The minimizing of uncertainty, the rift between what we think we know and what we suspect may be, while understandable, does not make our pursuits of knowledge more certain. Rather, it makes the limitations of our approaches insidious and more difficult to resolve.

Globalized and globalizing fields of knowledge-production present particular epistemological and practical concerns. Uncertainty has characterized many of the recent global health phenomena such as emerging epidemics like SARS and the H1N1 flu, attempts to quantify global pandemics such as HIV/AIDS or hepatitis C, or the potential impact of chemical or pharmaceutical products like DTT or Vioxx. Uncertainty results, it seems, from the sheer scale and mutability of health challenges, which thwart expectations for immediate redress. Institutions, practices, and ways-of-thinking that promise some form of knowing and order are understandably appealing (see McDonald 2000).
While the costs of mistakes in public health decisions are dire, the expectation that a singular paradigm will succeed in fully addressing health challenges is unhelpful. If we are to openly discuss the vulnerabilities of our approaches to public health decision-making, we must first renegotiate our relationship with uncertainty. Perhaps there is room for rethinking uncertainty as common rather than exceptional, and as productive rather than menacing. Where inefficiency or ill-will are frequently blamed for the failure of projects, perhaps there is room to consider the forgivable state of not-knowing without forfeiting a commitment to health rights or a sharp analytical perspective that is sensitive to market forces. Shapin and Schaffer write, “To identify the role of human agency in the making of an item of knowledge is to identify the possibility of its being otherwise” (1985:23). By cultivating uncertainty, we open avenues to more faithful and sensible sciences.

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ENDNOTES
1 Cost-effectiveness analyses compare the costs of two or more interventions in monetary units and their effectiveness in non-monetary units. Cost-benefit analyses, in contrast, compare interventions using only monetary units and are typically used to compare interventions for different clinical indications.
2 Medicines provided through SUS are divided into various categories or lists that indicate their cost, availability, and complexity. Essential medicines are the most widely available type in the system.
3 According to Health Net employees, several of whom had previously worked in SUS, such resource packages are frequently insufficient to cover a patient’s treatment, and public hospitals are perennially in debt as a result.
4 The employees who explained this spoke primarily from experience working in SUS. At the time, a company intern was working on a project to gather published or other-
wise written information on how precisely different forms of treatment were financed in different sections of SUS. I assisted with this project, which turned up few official or informative sources.

The Ministry of Health required that economic analyses be performed using SUS’s perspective, rather than from a societal perspective. A societal perspective may consider outcomes such as a patient’s lost productivity as a result of illness.

Head-to-head trials are designed to test different drugs under the same conditions in order to unequivocally demonstrate one’s superiority.

This sort of exchange is possible because hospitals frequently operate within SUS as well as for private insurers and patients willing to pay for procedures. As a result, a hospital may have newer drugs available for private patients but not for public patients.

While company employees could conduct analyses directly for the Ministry of Health from academic positions, and did, they could not as a private company.

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