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Maartje G. H. Niezen[1], Roland Bal[1] and Antoinette de Bont[1]

Abstract

This article's aim is to understand if and how the efforts to accumulate and organize clinical data transformed the regulation of pharmaceutical care. The authors analyze how the employment of databases by collectives of physicians and researchers shape both clinical and policy practice—and thereby reshape the relation between clinical work and policy. Since the late 1990s, Dutch government has supported the development of clinical databases for specific expensive medicines to gain oversight about actual medicine use. To be able to produce evidence for appropriate medicine use, the collectives set regulations in clinical practice. These internal regulations

[1] Erasmus University, Rotterdam, Netherlands

Corresponding Author:
Maartje G. H. Niezen, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
Email: niezen@bmg.eur.nl

provide a framework for establishing "appropriate medicine use", steering reimbursement decisions. However, internal regulation and policy rules differ in how quickly they can change. While the employment of databases in clinical practices results in a constant adjustment of the protocols, policy makers require the databases to provide for static moments of "proven appropriate medicine use" in order to account for and define a fixed and closed formulary. Subsequently, the employment of the databases did not deliver on the promise of oversight and control due to different clinical and policy requirements. Nevertheless, the databases did stimulate appropriate medicine use and reimbursement in clinical practice.

Keywords
regulatory objectivity, pharmaceutical regulation, databases

Introduction

Health policy is saturated in information technologies (Fox, Ward, and O'Rourke 2006; Roos, Menec, and Currie 2004). Paper-based records and scattered databases have been replaced by electronic records, data warehouses, and national population-based registries (Bowker 2005; De Mul, Adams, and de Bont 2009). As more and more clinical data are stored electronically, efforts to accumulate and organize it have increased. Furthermore, since it is now available in relatively easily accessible forms, clinical data have become both an object (something to be managed) and an instrument (something to manage with) and thus vital to a range of clinical, organizational, and governmental practices (Freeman 2002).

The aim of this article is to understand if and how the efforts to accumulate and organize clinical data and the increasing use of databases[1] in clinical, research, and policy practices have transformed the regulation of clinical practices. Data infrastructures such as databases mediate between clinical practitioners and regulators; the same data retrieved from clinical practice are used in clinical and policy practices and affects both. Databases can, first, facilitate self-regulation and quality assurance by national professional bodies, thereby allowing regulatory authority to be delegated to clinical practices (de Bont, Stoevelaar, and Bal 2007). They can also act as instruments of oversight. Data retrieved from local clinical practices can be stored externally in distant databases, which policy makers use for regulatory purposes (de Mul, Adams, and de Bont 2009; Waring 2007; Orr

2009). With access to detailed clinical data, policy makers believe they can impose order on clinical practice. For instance, health care policy makers can use clinical data to decide which therapies for which individuals should be reimbursed by health insurers.

This article's focus lies on how databases shape and are shaped by clinical and policy practices. Our empirical material comes from a study of the regulated use of pharmaceuticals in the Netherlands. Since late 1990s, the Dutch government has supported the development of clinical databases in order to gain insight and simultaneously construct evidence of the effectiveness of some expensive medicines in daily practice. In 2001, the Growth Hormone (GH) Database was the first clinical database employed to control the use of an outpatient drug. Similar databases have been developed for five outpatient medicines considered expensive at the time: antiretroviral therapy, paclitaxel, Interferon Beta, imiglucerase, and tumor necrosis factor-alpha (TNF-α) blockers.[2] In 2006, this form of regulation was extended to inpatient medicines. The Population-Based Haematological Registry for Observational Studies (PHAROS) is one of the first registries monitoring inpatient medicine use. The registry collects population-based data of especially new and costly treatments of three major haemato-oncological diseases, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, and multiple myeloma in daily practice. In this article, we reconstruct the employment of the GH Database and PHAROS registry.

The setup of the article is as follows. In the next section, we introduce the work of Beaulieu, Keating and Cambrosio, and Hine about the employment of databases. Their work provides a perspective to understand whether and how the use of databases reconfigures the relation between clinical and policy practices (Keating and Cambrosio 2004; Hine 2006; Beaulieu 2001). Instead of studying the contribution of information to science, policy, or practice, these studies focus on how technologies take part in and contribute to forming policy practices. As Keating and Cambrosio (2007) have described, science depends upon regulations, especially in fields where evidence is collected collaboratively—such as in pharmaceutical research and other fields in biomedicine (Keating and Cambrosio 2007). In these settings, "regulatory work" as embodied in the information infrastructures becomes a constitutive component of clinical work (Cambrosio et al. 2006; Keating and Cambrosio 2007). In the section on Regulatory Work in Clinical Practice, we reconstruct the regulatory work that was needed for the collective production of data. Moreover, we explore the use of internal clinical practice regulation for external oversight. In the section on Collective Internal Regulation and External Supervision, we aim to understand

how the way "evidence" or what is considered "objective data" is constructed, may lead to new forms of regulating medicines. We explore whether and how these new forms of regulation in clinical practice changed the relation between clinical and policy practice. In our discussion, we summarize our findings and argue that databases not only have transformed the regulation of clinical practice but have reconfigured and complicated the relation between policy and clinical practice too.

Regulatory Work and Objectivity

In this section, we take a closer look at the notion of objectivity to understand the intermediate role of databases between internal and external regulation of clinical practice. In her study on the Human Brain Project, Beaulieu (2001, 2004) shows how repositories shape and are shaped by a particular notion of objectivity—digital objectivity (Beaulieu 2004; Beaulieu 2001). Digital objectivity refers to a mechanism for the production and validation of knowledge (pooling data) making use of quantification, standardization, and automation, and a search for bypassing human judgment. According to Beaulieu (2001), digital technologies such as cameras, scanners, and computer technologies provide interfaces which prescribe or regulate how to work and handle data methodologically since they standardize and automate work practices. Subsequently, digital technology has led to the introduction of new elements of control and restraint. The digital atlas is not only a research tool combining and integrating the various versions of the brain produced by the different disciplines in neuroscience; it also is built up into data sets that have a normative potential. For example, the individual scan which varies from the norm is marked on a brain map (Beaulieu 2001).

Cambrosio et al. (2006) take a next step in the construction of what is considered "objective". By studying the collective production of evidence in biomedicine, they introduced the notion of "regulatory objectivity" (Cambrosio et al. 2006). The term regulatory objectivity refers to "a new form of objectivity (. . .) that generates conventions and norms through concerted programs of action based on the use of a variety of systems for the collective production of evidence" (Cambrosio et al. 2009, 654). The authors demonstrate that the work of biomedicine practitioners in the laboratory and the clinic depends upon a network of conventions that must be considered to conduct a single measure or to make a certain diagnosis. The conventions range from sometimes tacit and unintentional to formal modalities (Cambrosio et al. 2006, 2009). According to Cambrosio et al.

(2006), regulatory objectivity thus "turns the focus away from objects toward collective forms of expertise combining people (clinicians, researchers, administrators, patients, etc.) and objects (entities, instruments, tools, techniques, etc.) connected by specific coordination regimens" (Cambrosio et al. 2006, 194).

Digital and regulatory objectivity are distinct from other notions of objectivity, such as mechanical objectivity (Porter 1992, 1995), because of their unprecedented levels of reflexivity (Cambrosio et al. 2006; Keating and Cambrosio 2009). This reflexivity points at the deliberate and conscious formation of internal consensus on how to proceed objectively as part of the continual and endogenous development of regulation within (clinical) practice. Within the framework of regulatory objectivity, the process of reaching consensus is as important as the object of the resulting convention (Cambrosio et al. 2006). Medical professionals organized in groups across hospitals/institutions (and different from the professional associations) make collective agreements. These agreements, which are seen as the current state of evidence, get transformed into guidelines or standards. However, new scientific findings or new configurations of practices may open up the conventions previously taken for granted; the evidentiary hierarchies start changing and previously established agreements on the "evidence" are reopened (Thevenot 2009). The regulatory objectivity framework revolves around the configuration of shared rules of action in the submission, definition, and collective investigation of "uncertainty" (Cambrosio et al. 2009). The temporary agreements needed for internal regulation are under constant scrutiny and actors involved in the consensus process raise doubts about the reached "conventionality" based on, for example, ongoing research. It is exactly this uncertainty of the "conventionality" that glues the collective together and contributes to the dynamic and reflexive character of the process (Moreira, May, and Bond 2009; Rabeharisoa and Bourret 2009). In the following sections, we analyze the development of databases for the regulation of expensive medicines in the Netherlands to come to an understanding how such dynamic reflexive processes impact on clinical and policy practices.

Regulatory Work in Clinical Practice

Since the early 1990s, the Dutch government and its relatively autonomous agencies have undertaken much effort to regulate pharmaceutical care stringently, mainly by emphasizing the role evidence should have

in decision making on the appropriate use of drugs at all levels, from decisions on insurance schemes coverage to prescriptions at the point of care (College voor Zorgverzekeringen 2007; Commissie Dunning 1991; Gezondheidsraad 1991). The Dutch government has developed a series of tools to promote rational prescribing—such as professional guidelines authorized by state agencies, real-time monitoring systems, and expert committees that must authorize prescriptions—aimed at improving the quality and efficiency of care, and enabling the control of pharmaceutical health care expenditure (College voor Zorgverzekeringen 2005; Niezen et al. 2007). One specific measure is the conditional reimbursement regulation (Schedule 2 of Health Insurance Regulation[3]) which makes the reimbursement of particular medicines conditional to specific criteria or rules. For example, the use of medicines is restricted to specific categories of patients (e.g., based on indications) and/or place in treatment lines (e.g., step-up treatment).

Emphasizing the need for evidence-based policy allowed for the redefinition of ''appropriate use'' of medicines in terms of diagnosis, cost-effectiveness, and effectiveness as happening within clinical practice. This redefinition enabled decision makers to request data from clinical practice in the first place. Moreover, the new notion of appropriate use seems to have legitimized the regulation in the view of decision makers; it makes it more logical to keep track of a pharmaceutical's cost and effectiveness in clinical practice and to connect its additional funding to the delivered cost- and pharmaceutical effectiveness of care or categorization of diagnosis.

In this section, we take a closer look at the regulatory work in clinical practice and the use of internal clinical practice regulation for external oversight. We base our research findings on an exploration of two databases in the Netherlands: the GH Database and the PHAROS registry (on expensive oncolytics such as Ibritumomab tiuxetan and Alemtuzumab). Data on the two databases were collected in the form of individual interviews ($N = 61$) and focus group interviews ($N = 5$) with decision makers, health managers from the pharmaceutical industry, as well as health insurers, academic researchers, and medical professionals in the period 2003-2009. We audiotaped and transcribed verbatim the interviews as well as the focus group sessions. In addition, we observed conferences and informal meetings, and analyzed minutes, e-mail exchanges, and policy documents including documents from archives of the main policy actor, the Health Care Insurance Board (College voor zorgverzekeringen [CVZ]).

Regulating GH

In 1998 it became possible to produce GH outside the human body. As a result, GH turned from a scarce drug into an expensive drug. Subsequently, policy makers requested GH monitoring. Not only because the treatment is expensive (€23,000 per treatment per year in 2004) but also because the number of treatments could increase. GH treatment is indicated foremost for children with growth hormone deficiency (GHD), whose bodies do not produce sufficient GH (somatotropin) levels which results in growth failure. The treatment, however, could be broadened to other indications than GHD.

In an attempt to control costs, a clinical guideline focusing on the diagnostic criteria to determine GHD was authorized by CVZ. Since health insurers are only allowed to cover GH treatment if patients are diagnosed and treated according to this authorized guideline, the diagnostic criteria derived from clinical research and experience (the professionals' guideline) became a policy tool. Additionally, clinicians were obliged to lodge patient data in a national GH Database—a former multicenter trial database—including laboratory test results, dosage, and possible tumors, managed by the National Registration of Growth Hormone (Landelijke Registratie Groeihormoonbehandeling [LRG]).

The GH database shows how data registration represents a mechanism for the production and validation of knowledge.

> Respondent 1: Here it [GH registration] is a combination of prevention of excessive use of an expensive medicine with the simultaneous collection of an amount of knowledge on such a medicine [GH] which is also useful, and which can diminish its use in the future. For example, now we see that the dosages go down. (Medical professional, 2003)

Regulation of appropriate medicine use thus required pooling data from individual patient records into a national database and subsequently allowed for gaining knowledge on GH dosages. Moreover, lodging patient data in the GH database required the quantification and standardization of clinical practice. Previous diagnostic criteria were transformed into numerical thresholds, determining the different patient categories by severity and likelihood of GHD (Table 1).

The registration of data on GH diagnoses and prescription in a database not only allowed for the production and validation of knowledge, it also introduced an element of control. The obligation of data lodging made it

Table 1. Patient Categories by Severity of Growth Hormone Deficiency and Likelihood of Growth Hormone Deficiency (GHD).

Patient Category	Technical Description	Likelihood of Diagnosis GHD
Category 1	Very low maximum GH level (<5 mE/l) and very low IGF-1 or IGFBP3 <P3	Certain
Category 2	GH peak value <10 mE/l en IGF-1 of IGFBP3 <P50.	Almost certain
Category 3	Combination of GH peak value <10 mE/l and IGF-1 of IGFBP3 >P50 or GH peak value 20–30 mE/l and IGF-1 of IGFBP3 <P50	Probably partial deficiency
Category 4	GH peak value 20–30 mE/l and IGF-1 of IGFBP3 <P3	Possibly partial deficiency
Category 5	GH peak value 20–30 mE/l and IGF-1 or IGFBP3 between P3 and P50.	Low probability
Category 6	GH peak value >20 mE/l and IGF-1 or IGFBP3 >P50	Unlikely
Category 7	GH peak value >30 mE/l and IGF-1 or IGFBP3 <P3	Probable Laron-type dwarfism

Source: Ziekenfondsraad 1997.

possible to control the diagnosis and reimbursement of GH treatment. The patient record changed from "notes" on a patient's condition to "obligatory fields" to fill in. Only when all the boxes are checked and the diagnosis is made according to the predefined categories, will a patient receive pharmaceutical treatment with GH. Patients placed in categories 1–4 in Table 1 should be treated with GH and their treatment is eligible for reimbursement (Ziekenfondsraad 1997). A specialists' forum should make the decision for patients in category 5, as the diagnosis of GH deficiency is less certain for these patients. All requests for treating patients in categories 6 and 7 should be rejected. With data retrieved from the patients records it becomes possible to check whether patients treated with GH are classified in categories 1–5 and that none of the patients receiving GH are actually in categories 6 and 7 (see Table 1).

> Respondent 2: ...I mean, nowadays it is so easy ... It goes into the computer and then you can work on, look at and do things with [the data] ... ehm, I think that is the right thing to do since each clinic only has a limited amount of patients. Therefore we don't know how patients are treated

> overall in The Netherlands, or how we perform as pediatricians, for example, in growth hormone treatments. (Medical professional, 2004)

The formalization of clinical (research) practices has brought database use into the decision-making process and has enabled the development of control functions within medical practice that were formerly located in the realm of policy. The database forms part of the work needed to "objectify" clinical work.

Regulating Oncolytics

In 2006, conditional reimbursement regulation was extended from outpatient medicines to inpatient medicines through the High-Cost Medicines Policy Regulation (Beleidsregel Dure Geneesmiddelen [BDG]).[4] The BDG regulates the additional funding of hospitals for expensive medicines. Importantly, this regulation includes evidence development on the effectiveness and cost-effectiveness of listed medicines in clinical practice after market approval. The BDG was installed to speed up the introduction of new inpatient medicines. New treatments for patients with haematological malignancies are constantly introduced and are also subject to ongoing adaptations (e.g., different doses, introduction at other treatment stages and in new combinations with other treatments). To counter the rapid introduction and reimbursement of these new medicines, policy makers ensured that the BDG was introduced with the prerequisite to keep open the option to reconsider earlier reimbursement decisions. Whereas in the past the regulation of expensive medicines was based on the (modeled) outcomes of trial research and fitted within a "yes" or "no" reimbursement regime, the BDG shows a new and broader view toward the assessment of appropriate medicine use. It is based on ongoing data retrieval from clinical practice demonstrating effectiveness in daily practice. The conditional listing is used by policy makers to collect "missing" data to decide on a pharmaceutical's effectiveness in practice and on further reimbursement. Data must be collected for three years on a medicine's cost-effectiveness and effectiveness in clinical practice (College Tarieven Gezondheidszorg 2002; Nederlandse Zorgautoriteit 2006; Nederlandse Zorgautoriteit 2008).

Like the GH Database, PHAROS is built upon an existing registry—a regional cancer registry that is part of the Dutch Cancer Registry—in combination with follow-up data retrieved from medical records. Oncolytics thus have a history of registration in medical practice and

will continue to be registered. Since 1989, the Dutch Cancer Registry has been collecting data on cancer patients in order to map the national occurrence of cancer (see http://iknl.nl). The regional cancer registry contains medical data on the patient's disease and treatment (tumor identification, diagnostics, and treatment) and administrative data concerning other characteristics (name, date, address, etc.) of all cancer-diagnosed patients from the cooperating hospitals in the region.

> PHAROS will look at the influence of newly introduced diagnostic- and therapeutic developments on the care delivery process and its outcomes. (. . .)
>
> PHAROS serves for scientific sound reporting on the amount of influence newly introduced so-called expensive medicines have on costs and especially benefits. This way, the data in PHAROS can also be used for cost-effectiveness analysis, as meant by the High-Cost Medicines Policy Regulation. (Uyl and Huijgens 2009, Description Pharos project translated by MN)

The data stored in PHAROS enables the detection of trends in diagnostics, treatments, treatment results, and survival for patients with haematological malignancies. PHAROS also enables the analysis of the effective use in daily practice of two high-cost medicines: Ibritumomab tiuxetan and Alemtuzumab.

> Respondent 3: Most important is that the medical professionals are provided with a tool [the PHAROS database] that can enhance the quality of care. And suppose this database shows that in average only three courses of treatment with medicine X are provided . . . that is rather remarkable since the label states that eight courses should be given. These are the kind of munitions which medical professionals can use to discuss appropriate treatment. Thus, a database can enhance the quality of care and simultaneously allow for monitoring whether treatment according to guidelines occurs. If there is no guideline adherence, the medical professionals should discuss whether the provided treatment is inappropriate or guideline adjustments are required. (Employee Pharmaceutical Manufacturer, 2008).

With the PHAROS databases, physicians took on the obligation to achieve results that matched with the results of a clinical trial. As shown in clinical trials, appropriate drug use can only be achieved in clinical practice if the same or similar guidelines are followed and similar patient groups are selected. Yet in the particular context of Ibritumomab tiuxetan and Alemtuzumab used in tertiary cancer care (PHAROS)—and most other cancer treatments on the BDG list—

medical practice is already highly regulated and preregistration research is highly protocolized. Therefore, the difference between the regulations in trial settings and clinical practice is relatively small.

> Respondent 4: In some cases the situation in clinical practice is so controlled, for example with regard to the haematological diseases, you can almost say it matches a randomized clinical trial. The patients are so tightly monitored that the border between clinical practice and an experimental setting just isn't that hard anymore. (Policy maker CVZ, 2008).

The protocols used for Ibritumomab tiuxetan and Alemtuzumab in clinical trials are also used in daily practice after their market authorization and thus continue to dominate the use of oncolytics in clinical practice after their registration. However, the effectiveness in daily practice differs from the trial settings due to, for example, more variation in the patient groups and more importantly ongoing insights in pharmacotherapy. It is such differences, alongside the continuation of data collection, that are the object of continuous reflection.

PHAROS combines clinicians, researchers, and so on from various disciplines in order to reflect upon, shape or adjust the conventions and regulations in clinical practice, with the aid of objects such as information systems combining clinical and administrative data, protocols, and methodologies. The PHAROS data and conventions are discussed at least twice a year by the various actors in the PHAROS collective.

> Respondent 5: The steering committee on the data registration of expensive oncological medicines meets once every six to eight weeks. Professor Z takes her two PhD-students with her and together we take a look at the data generation and registration . . . The committee also includes representatives from the Health Care Insurance Board [CVZ]. (Medical professional, 2008)

These discussions not only lead to innovative treatments but also give shape to an innovative form of regulating clinical practice. To assure quality of treatment as well as maintain both up-to-date and effective treatments, the PHAROS collective depends upon an arrangement of conventions (data collection, data analysis, and discussion) which must be considered when prescribing or adjusting appropriate doses of Ibritumomab tiuxetan and Alemtuzumab, possibly in combination with other treatments. What is considered up-to-date, effective and assured quality of treatment has become the subject of formal regulations and reflections.

Externalization of Regulatory Work in Clinical Practices

It may not be a coincidence that both databases we explored are used to control already highly regulated medicines. Prescribing these expensive medicines is often preserved for specialized medical centers. Highly protocolized health care practices, such as GH treatment and tertiary cancer care, enable the collection of standardized data. In both cases, the data registries predated the government's prerequisite of data collection for financial compensation. In fact, the development of both databases is closely connected to the development of guidelines and protocols. The GH guideline has been developed at the request of the Dutch Minister of Health in order to ensure the GH treatment was provided appropriately, meaning, according to the conditional reimbursement regulation. This official national GH treatment guideline mainly determined what data are collected in the GH Database (1998-2001). Therefore, while the definition of the different patient categories for GH treatment (Table 1) points to a situation which is both protocolized and easily quantifiable, it actually is the result of much foregoing work; the bureaucratic innovation preceding the development of data collection technologies (Bowker 2005). Similarly, the tertiary cancer care involves much preregistration research, which requires highly protocolized practices. Therefore, it may not be coincidental that most of the medicines listed in the BDG are used in cancer treatments (seventeen of the thirty by October 2008). In this way, government regulation is based on the regulatory work of the clinic which is assessable through guidelines, protocols, and data collection. Both cases depict a history of regulatory work, the registration of clinical data, and prior bureaucratic innovations such as guideline development within clinical (research) practice. Data registration merely has facilitated the externalization of the regulatory work already inherent and constitutive to clinical practice (Keating and Cambrosio 2004; Cambrosio et al. 2006; Keating and Cambrosio 2009).

Collective Internal Regulation and External Supervision

It appears that regulatory authority is delegated to a network of physicians who achieve control by self-regulation and uphold quality assurance. Would the presence of internal regulation and the externalization of the regulatory work within clinical practice allowing for policy makers to supervise appropriate pharmacotherapy and its reimbursement

then mean that the gap between policy and practice has been bridged? In this section, we explore whether and how databases changed the relation between clinical and policy practices, using the GH and PHAROS cases as an example. In particular, we focus on how databases construct "evidence" or "objective data" potentially leading to new forms of regulating medicines. We follow the dynamic process of the constant adjustment of conventions on appropriate medicine use within clinical practice and its relation to the construction of evidence informed reimbursement regulations.

Adoptions in GH Guidelines and Reimbursement Decisions

The GH case shows how the collective shaping of clinical practice regulation was formed around the uncertainty of unknown side effects of GH treatment. Dutch paediatric endocrinologists meet four times a year in the Advisory Group on Growth Hormone (AGH). On the request of the AGH, the LRG analyses the GH database data. The LRG, for example, compares all patients with partial GHD and reports on the clinical results of their treatment. These data are then fed back into the guideline-development process. Draft revisions of the guideline are discussed with all paediatric endocrinologists in the Netherlands at their annual meetings. The purpose of these discussions is to reach shared agreements on best practice. If these agreements are reached, all paediatric endocrinologists receive an update or a supplement to the guideline. The following two quotations depict how the diagnostic criteria of GHD and its categorization have become the subject of clinical practice's reflexive assessment.

> Respondent 6: There's also much debate on . . . Let's put it this way, there's a lot of discussion whether you should treat all people who meet the criteria. That is what is heavily debated.
>
> Interviewer: Where do these debates than take place?
>
> Respondent 6: Ehm, mostly on conferences and within the literature. The question is if someone who meets the standard criteria . . . , who, according to the tests, of which I believe the ITT is de most important test, is eligible for growth hormone treatment, should also be given the growth hormone. (Medical professional, 2004)

The GH database allowed for internal consensus on how to proceed objectively as part of the continual and endogenous development of regulation within (clinical) practice.

> Respondent 7: The indications have shifted. For example, if we think this is a neurosecretory dysfunction we used to have a problem with how to act upon this, what norms we should use and so on. Well, at a certain point in time the Advisory panel Growth Hormone has documented this; this is the way we define neurosecretory dysfunction in The Netherlands. When in doubt a growth hormone profile should be made. In the past these growth hormone profiles in turn would be point of discussion; "What are the normal values? Is there a difference between laboratory results?" Well, these normal values have been documented and the laboratories have been brought into line. In this sense, the GH database has offered a clear threshold. (Medical professional, 2004)

In 2005, the LRG presented more detailed data about patients who use GH (see Table 2). In the report to CVZ, the professionals concluded that 2 percent of the patients treated with GH should not have received the drug according to the guideline. The policy makers disagreed. According to them, 13 percent of the patients did not meet the formal indication criteria for GH treatment and thus reimbursement. Whereas the policy makers compared the decisions to treat patients with the predefined decision framework—the published and authorized guidelines—the professionals referred to the most recent guidelines. Over the years, professional norms and more specifically the guidelines shifted as scientific work progressed. The database and its infrastructure allowed for the continual adaptation, updating, and modification of the side effects and diagnostic categories. Accordingly, the technical description of the patient categories and the likelihood of diagnosis GHD changed. Subsequent to a new indication, the professionals adjusted their clinical guidelines whereupon the first authorized GH guideline became outdated, as the LRG explained. This continual and reflexive assessment of the uncertainty around the formation of GH regulation is endogenous to and essential for the dynamics in the GH network. Yet, CVZ insisted that 13 percent of the decisions to treat GH were inconsistent with existing regulations. Despite requests for more explanation and additional investigation and several meetings, policy makers and professionals did not come to an agreement. Regardless of the formal national regulations the professionals seemed to feel it was unthinkable to go against their professional norms. CVZ took the opposite stance and seemed to find it unthinkable to go against national regulations, especially as the professionals

Table 2. Distribution of Decisions According to CVZ Authorized and Updated Professional Guideline.

Diagnosis	Categories	Distribution Of Patients According to CVZ Authorized Guideline (%)	Distribution of Patients According to Updated Professional Guideline (%)
Certain GH deficiency	Categories 1–4	84	96
Uncertain GH deficiency	Category 5	2	2
Certainly no GH deficiency	Categories 6 and 7	13	2

Note: GH = growth hormone.
Source: de Bont, Stoevelaar, and Bal 2007.

shifted their norms without informing policy makers and patient representatives.

CVZ had no problem understanding the explanation given. The problem was, as a CVZ employee explained in an interview, "how to rule when the rules change."

With the introduction of the GH database, meant to supervise and regulate clinical practice, the relation between CVZ and the professionals became less defined by the interpretation of the regulations and more by standards and the knowledge of professionals as embedded in the database and translated to updated guidelines. Not only did regulations change guidelines, the guidelines also changed the regulations. With that, new adoption problems between policy and practice emerged. In the GH case, the collective production of evidence ultimately, rather than bridging the divide between clinical and policy practice, rearticulated the relationship between the two in terms of differing time frames or, more specifically, in a dichotomy between dynamic and static regulations.

The Process of PHAROS Data Registration and Policy Decisions

In the PHAROS case, policy makers had learned from the GH case and changed coordination practices accordingly. In order to cope with the constantly changing regulations in clinical practice, CVZ decided not to steer by the outcome of regulation as with GH but by its process. Therefore, the configuration of the evidence informing appropriate medicine use and reimbursement in practice should be a derivative of the data collected and registered in a database in the three-year research period by the collectives of

researchers, medical professionals, and pharmaceutical industry. By focusing on the regulatory process in clinical practice, CVZ acknowledged the dynamic nature of clinical research and practice.

> Respondent 4: When pharmaceutical industry and medical profession apply for additional reimbursement we do not ask to just provide [cost-effectiveness] data, we only say: "explain how it should be ... provide an indication of the medicine's efficiency". And, when they explain how they will collect data on and research the (cost-) effectiveness of the medicine in clinical practice, then, in essence we are done for t=o [Start of the research period MN]. And then, in essence the product can be admitted in the policy regulation. Only after three years we look at the provided evidence in order to give us the feeling that it can be uphold [whether the medicine's additional reimbursement should be continued]. (Policy maker CVZ, 2008)

In the PHAROS case, CVZ did not define a prior decision framework or threshold but focused on how to use data collection as a reflexive instrument for clinical practice. Moreover, whereas within the GH database, the medical professionals solely decided what data were lodged in the registry, in PHAROS, other stakeholders such as the pharmaceutical partners, The Netherlands Organization for Health Research and Development[5] and CVZ were able to codecide what data should be collected.

> Respondent 8: That is why we decided in yesterday's meeting by telephone [with the pharmaceutical manufacturers and professor Y of the comprehensive cancer center] to write a letter to The Netherlands Organisation for Health Research and Development in which we state not to agree upon the proposed research construction. We want to maintain the population based registry. We will include some detailed data because the Health Care Insurance Board [CVZ] is also interested in over- and under dosages. The pharmaceutical industry has asked this question which is based on their experience in earlier dossiers. The clinicians preferred not to include these data, however after a separate phone call with the Dutch Cooperative Group on Haemato-Oncology they have agreed upon this. (Professor in health technology assessment, 2008)

CVZ decides what evidence is required to determine their effectiveness in daily practice, which type of test provides acceptable evidence and how it will be judged and by whom. These data are used to steer clinical

practice. In turn, the data available for collection in clinical practice determined the kind decisions the policy makers can made.

However, despite the "common language" offered by PHAROS and its focus on the process of data collection, it did not reduce the distance between policy and practice. In the end, CVZ is expected to account for the continuation of reimbursement of an expensive medicine after the process of data collection is or should be finished (BDG allows for a three-year period of data collection). It was expected that more dynamic regulation would follow dynamic clinical practice, yet would allow for the control of cost-effectiveness in medicine use too. CVZ, however, has to freeze this dynamic process at a particular moment in time to make choices based on the process of data collection and the evidence provided thus far. Whereas clinical practice regards evidence as "in process," policy makers must treat the information as an available outcome, at least at the moment a decision has to be made. This pressure for transparency and accountability for the additional and conditional funding of expensive medicines comes not only from the political context (democratic legitimacy) but more importantly also from the pharmaceutical industry which lobbies government to steer on outcomes and prior defined decision frameworks and thresholds.

> Respondent 9: And how will we distinguish later on ... the situations of which we believe the applicants have a good report on the process of data collection, that allow for regulating (cost-) effective use in clinical practice, but lack outcomes and therefore are given the benefit of the doubt. Of course we need to try to maintain that group of medicines as small as possible. So, the group 'yes' [inclusion in the regulation MN] should be as big as possible as well as the club of 'no'- decisions. The grey area in between should be as small as possible. (Policy maker CVZ, 2008)

At that point, the focus of CVZ changes from process to outcomes. The outcomes are modelled by means of health economic methodologies into the best prediction of long-term effects and cost-effectiveness, and so on. At this point precisely, policy and clinical practice rearticulate their relation in the form of the static-dynamic dichotomy. The regulatory environment of policy requires ending the process of data analysis as the focus is on fixed categories to account for and decide upon appropriate medicine use and reimbursement. In contrast, the regulatory environment of clinical practice requires further data analysis as it focus lays in gaining new insights (e.g., in patient categories or dosages) and address uncertainties in appropriate medicine use.

Discussion

In this article, we sought to analyze how the use of databases has transformed the regulation of clinical practices through case studies of the Dutch GH and PHAROS databases. The Dutch government requires physicians to collect clinical data into a database as a condition for the reimbursement of certain, expensive drugs. The government supported the development of drug databases to gain oversight in prescription and reimbursement practices. The ideal of appropriate drug use, however, is reached not so much through direct steering based on the outcomes of the databases, but indirectly by stimulating data collection and the continuous reflection upon the data by researchers and clinicians. These internal regulations provide a framework for establishing the ''appropriate medicine use'' on which to base decisions on pharmaceutical reimbursement by health policy regulators. Without the demand for data collection through the conditional reimbursement regulations, this process of clinical practice regulation would have remained implicit and more importantly have less connection to the realm of health policy. Moreover, since health policy regulators codetermine what data should be collected, they are able to steer what information the medical professionals use to inform their practice. The databases are in this way coproduced by the collectives of clinicians, researchers, and policy makers who set regulations in clinical practice about what is considered appropriate medicine use.

Did the presence of internal regulation and the externalization of the regulatory work within clinical practice mean that the gap between policy and practice has been bridged? Not so. Rather, the existence of regulatory objectivity in clinical practice added further complexity to the relation between policy and practice. Rather than bridging the policy-clinical practice divide through the collection of data or through the delegation of regulated authority to clinical practice, the continual process of reflection of appropriate pharmacotherapy let to new frictions. Regulations within clinical practice are formed in response to the constant adaptation, updating and modification surrounding the uncertainties of pharmaceutical treatment. The collectively determined conventions only temporarily provide closure on the uncertainties related to the effective use of expensive pharmaceuticals in daily clinical practice (Cambrosio et al. 2009). The ''closed'' uncertainties are continually challenged because of the clinicians' reflexive use of data in the databases in combination with their experience in daily practice. Clinical work has become integral to regulatory bodies such as CVZ, and regulatory bodies have become integral to the dynamics of clinical practice

(cf. Cambrosio et al. 2006; Hogle 2009). Yet, the ultimate goal of the current policy regime thus far remains a stable and closed list with reimbursable drugs. Whereas regulations in clinical practice are continually being reshaped, governmental practices—because of the need for accountability—still require some static moments of "proven appropriate medicine use." In fact, the requirement of databases in the new conditional reimbursement regulation has stimulated the dynamic and ongoing process of data collection and interpretation in clinical practice. However, the actual policy decisions to be made in the end require the closing down of this process in a single "yes" or "no" decision about reimbursement. Moreover, the reimbursement regulation is monitored as if rules did not change, despite decision makers' intention to allow for a dynamic regulation.

As our research on the evolution of databases as regulating instruments provides a glimpse of the period 2004-2009, it will be interesting to see how data collection for regulating purposes develops in the future, especially in the field of innovative medicines. Professional networks developing around the regulatory medicinal- or population-based databases will gain in importance, similar to the increasing importance of in benefit package management. This form of coordination is about to define key areas of medical governance (ACP meeting, Health Care Insurance Board, September 11, 2009). The cases we studied have made some steps toward this. Compared to the collectives using the GH database, PHAROS shows an increasing focus on the process of data collection and reflection. This widening of the governmental focus has led to a more dynamic regulatory environment in both policy and clinical practices. Regulating pharmaceutical care via databases is a promising approach for stimulating appropriate medicine use and reimbursement. Especially when the focus is maintained on the continual process of collective production of evidence, combining data provided by the databases and reflections on the data collection, regulatory tools such as guidelines or models of action will be produced stimulating appropriate medicine use and reimbursement in clinical practice. However, legitimating policy decisions currently stands in the way of such dynamic practices as they imply fixing "appropriate medicine use" at a particular moment. Whereas initially policy makers believed databases promised insight in clinical practice and subsequently control, the PHAROS case provides a glimpse of the renewed promise of databases and regulation of "appropriate medicine use." In the PHAROS case, CVZ tried to shift focus from health outcomes toward a process of evidence building and the constant and dynamic adjustment of pharmaceutical care regulations. This dynamic process of continual data collection and reflexivity by medical professionals

and researchers fulfilled the health regulators' goal of stimulating appropriate medicine use and reimbursement in clinical practice during the three-year period of data collection. However, the current Dutch legislation does not (yet) allow for such a shift, since it is based on an "in" or "out" logic of benefit package management.

We should be aware that not all medical practices can be regulated through this new form of governance – coverage with evidence development through data collection in clinical practice. Especially in clinical practice settings where data are less likely to be registered as part of clinical work, one should be hesitant about governing (pharmaceutical) care through data collections. For example, conditional reimbursement of statins (cholesterol-lowering medications) has already been shown to be rather problematic and most likely this will also hold true for medical aids (Niezen et al. 2007; Zuiderent-Jerak and Van der Grinten 2008). An implication for clinical practice is that eligibility for additional funding based on the prerequisite of data collection depends on the degree of regulatory work already existing in clinical practice. Both of the databases we analyzed existed prior to the policy requirements to collect data. Rather than developing new databases, the policy makers built this existing infrastructure. They stimulated and subsidized the development of the databases to inform regulations. In the event conditional reimbursement and its prerequisite of data collection increases in importance as a policy tool and the requirements concerning the effectiveness in clinical practice increase, we expect the less protocolized clinical practices will find eligibility for funding more difficult. In this event, other types of governing care might have a better fit.

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Notes

1. The concept "databases" in this article can be seen as a synonym for "data registries." Whereas in the field of outcome research, one prefers to speak of data registries, we have chosen to use the concept of "databases" as used within Science and Technology Studies. It refers to the infrastructure allowing for the collection and processing of data as well as the data stored in these databases.
2. For the treatment of HIV (antiretroviral therapy), lung, ovarian, breast cancer, head, and neck cancer, advanced forms of Kaposi's sarcoma and the prevention of restenosis (Paclitaxel), multiple sclerosis (Interferon Beta), Gaucher's disease (imiglucerase) and rheumatic arthritis, Crohn's disease, psoriasis, and colitis ulcerosa (TNF-α blockers), respectively.
3. The Health Insurance Regulation regulates the execution of the Dutch Health Insurance Act (ZVW).
4. The High-cost Medicines Policy Regulation (Beleidsregel Dure Geneesmiddelen: BDG) is maintained by the Dutch Health Care Authority (NZa) and is based on Article 57 of the Health Care Market Regulation Act (WMG).
5. The Netherlands Organization for Health Research and Development (ZonMW) manages the subsidies for the process of evidence building (databases) required by the BDG.

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Author Biographies

Maartje G.H. Niezen, MA, is a social scientific researcher in pharmaceutical policy and formulary management at Erasmus University Rotterdam, The Netherlands. Her doctoral research studies the employment of knowledge infrastructures and policy instruments in decision making, with a specific interest in steering the control and use of pharmaceuticals. She appeared in *European Journal of Cancer, Health Policy* and *International Journal of Technology Assessment in Health Care.*

Roland Bal is a professor of Healthcare Governance at Erasmus University Rotterdam. His research interest is the governance of quality and safety of healthcare and science and policy relations. His latest book, Paradox of Scientific Authority, co-authored with Wiebe Bijker and Ruud Hendriks, was published with MIT Press in 2009.

Antoinette de Bont is an associate professor of Healthcare Governance at Erasmus University Rotterdam. Her research interest is the governance of quality and safety of healthcare, with a specific interest in information technology and information science. She was the principal investigator of this study.