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Health technology assessment and ill-structured problems: A case study concerning the drug mebeverine

Margriet Moret-Hartman, Gert Jan van der Wilt
Radboud University Medical Center

John Grin
University of Amsterdam

Objectives: The practical significance of health technology assessment (HTA) in policy decisions or clinical practice has been challenged. Possibly, problem definitions underlying HTA do not concur sufficiently with the problem definitions held by policy makers or clinicians. We performed an in-depth case study on mebeverine, a drug prescribed to patients with irritable bowel syndrome, to explore this hypothesis.
Methods: The theoretical framework was provided by the theory of argumentative policy analysis. We analyzed documents and held semistructured interviews to collect data. We reconstructed interpretative frames to analyze actors' argumentation.
Results: The funding and usage problems relating to mebeverine were ill-structured. Actors disagreed on the information needed and the norms at stake. As a result, the problem definition shifted, and the resulting problem definitions failed to correspond with the problems perceived by the target populations.
Conclusions: To ensure that future studies on healthcare problems are useful, it is imperative that policy makers take the problem definitions of potential users into account.

Keywords: Health technology assessment, Ill-structured problems, Case study, Irritable bowel syndrome

Health technology assessment (HTA) generally aims to support healthcare policy making (1). However, the actual contribution of HTA to the policy-making process has been questioned (15;28). It is possible that HTA provides its users (policy makers) with insufficient insights on the considerations and life worlds of the target populations that will be affected by potential policy measures. Such insights are needed because, in health care, policy has shifted from central regulation to an approach based on target populations. The focus is currently placed on influencing the doings and dealings of patients, physicians, and other target populations (4;11;21;24;25;30). Policy problems can be formulated differently by the actors involved because information that surrounds these problems can be interpreted differently (8).

Literature on argumentative policy analysis (10;17;32) contends that to acquire the cooperation of target populations (crucial for effective policies), the perspectives of the target population must be taken into account during the development of policy. For instance, with respect to policies aimed at promoting sustainable development, target populations cooperate if, and only if, they consider the proposed policy measures to be meaningful. A measure is considered meaningful when it corresponds with their problem definition and does not conflict with their background theories or preferences (32). Consequently, policy research should take the problem definitions of its users and target populations

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and the meaning they attribute to potential policy measures into account.

We examined a case of policy research on mebeverine, a drug frequently prescribed to patients with irritable bowel syndrome (IBS). Patients with IBS suffer from diarrhea, constipation, or spasms of the gastrointestinal tract for which no structural or biochemical cause can be found. The drug is thought to affect smooth muscle cells in the colon and is, thus, expected to relax the muscles and thereby decrease spasms (6;12;26). Although the drug is frequently prescribed, there is discussion regarding its effectiveness (23). The uncertainty about the effectiveness of mebeverine has also been a relevant issue in Dutch reimbursement decisions. In particular, mebeverine seemed to be a drug that could easily be removed from the public healthcare package. After failed policy, new research was proposed to inform future policy measurements on this subject. Unfortunately, the commissioner considered the outcome of a preliminary study not useful for further policy measures. As a result, no further policy measures were taken.

The aim of the present study was to explore the extent to which the failures in policy and subsequent policy research may have resulted from incompatible problem definitions among various stakeholders. The research questions were: How did the process of policy analysis and subsequent research proceed? Who was involved and how did they define the problem? Did the study incorporate problems perceived by target populations (physicians and patients) with respect to policy measures?

METHODS

The theoretical framework used in this study was argumentative policy analysis. This theory contends that successful implementation of policy requires the cooperation of the target populations. Target populations are actors who are likely to experience the consequences of the intended policy; and actors whose cooperation may be necessary for successful implementation. Cooperation from these target populations is more likely if they consider the proposed measures meaningful. This means that they expect the measures to provide a solution to problems they perceive.

We used the method of reconstructing interpretative frames to analyze target populations' argumentation (14). One's interpretative frame is composed of problem definitions and judgment of possible solutions, but also the empirical and normative background theories that shape them (13;31).

We analyzed documents and held semistructured interviews to collect data. First, we analyzed the process of policy analysis and the subsequent research project retrospectively. Data were obtained from the file on this project in the archive of the Heath Care Insurance Board (HCIB). The file contained letters, reports from the Board, internal memos on this subject, research proposals, and a research report. Second, semistructured interviews were held to reconstruct actors' perspectives. Interviews were held with policy makers, researchers, physicians, and patients. We prepared for interviews by conducting a detailed analysis of the existing literature on mebeverine and irritable bowel syndrome. In the interviews, the questions focused on perceived problems and reasons for actions or decisions. The actors involved in the project (two policy makers from the HCIB and two researchers) and a policy maker from the Ministry of Health were asked provide reasons for the specific choices that were made during the process of policy analysis. Members of target populations (two general practitioners, one gastroenterologist, and two patients, who were founders of the IBS patient association) were asked about their use of mebeverine, their reasons for using this treatment, alternative treatment strategies, ideas about IBS, and perceived problems relating to the care for IBS patients.

Interviews were transcribed verbatim and coded. Four layers of one's interpretative frame and relevant subjects were distinguished. The interview transcripts and a conceptual version of the report were sent to respondents for comment (respondent validation).

RESULTS

In this section, we first describe the proceedings of the policy analysis. A summary of the problem definitions and possible solutions at several time intervals is also provided in Table 1. Second, we compare policy-makers' perspectives with the perspectives of target populations.

Reconstruction of Policy Analysis Proceedings

In 1996, drugs in the Dutch public healthcare package were screened on the basis of the need for and effectiveness to develop a high quality and affordable healthcare package. The Ministry of Health asked the Sickness Funds Council (currently called the Health Care Insurance Board) for advice on several drugs, including mebeverine. The Ministry did not consider mebeverine to be very effective. Other interventions, such as dietary advice and reassurance, were considered more efficient.

In response to the Ministry's request for advice on the reimbursement of drugs, the Sickness Funds Council developed a decision model (34). The criteria for assessment included the efficacy, effectiveness, therapeutic value, and efficiency of the drug in question (Table 2). With respect to mebeverine, the Council concluded that (i) the efficacy of the drug was assessed when mebeverine was initially registered, (ii) convincing evidence on the drug's effectiveness was lacking, and (iii) its therapeutic value is limited. Despite the apparent limitations, the Council recommended that the Ministry continue to reimburse mebeverine, because the Council deemed it advisable to have at least some form of medicinal treatment

Table 1. Problem Definitions and Proposed Solutions

	Problem definition	Solution
Advice Sickness Funds Council (September 1995)	Effectiveness of mebeverine is disappointing	Strict administration of the protocol leads to exclusion from the healthcare package; however, because of symptoms and lack of alternatives, it should be reimbursed until further notice
Ministry of health (December 1995)	Mebeverine has little therapeutic value; other interventions more efficient	Mebeverine should be excluded from reimbursement
Policy document PAM (March 1999)	Mebeverine is reimbursed, however, still questions on its efficacy or effectiveness remain	Research on the effectiveness of mebeverine
Letter covering the PAM policy document (March 1999)	The industry made the court pass a sentence on the efficacy of mebeverine. However, efficacy does not lead to effectiveness automatically	Question on the effectiveness of mebeverine still needs to be answered
Policy document PAM (April 1999)	Unlikely that trial results will be useful to remove mebeverine from healthcare package	Aim should be to act on prescribing patterns. Research on therapeutic value of mebeverine
Proposal researchers (June 1999)	—	Preliminary study on the feasibility of a trial on the therapeutic value of mebeverine
Final report researchers (November 1999)	Evidence on IBS treatment is lacking	A trial on the efficacy of mebeverine and fibers is feasible
Policy document PAM (January 2001)		European tender of placebo-controlled trial on effect of mebeverine
Comment advisory committee PAM (January 2001)	Previous studies on the effectiveness of mebeverine were methodologically flawed	Impossible to prove effectiveness mebeverine in trial
Report Health Care Insurance Board (February 2002)		No randomized controlled trial on the effectiveness or therapeutic value of mebeverine

PAM, Department of Policy Analysis of Medicines; IBS, irritable bowel syndrome.

Table 2. Reimbursement Criteria (34)

Criterion	Description
Efficacy	Its pharmacological action results in a therapeutic effect in clinical research (therapeutic potential)
Effectiveness	Its use in clinical practice results in the aimed goal of the treatment
Therapeutic value	The sum of its relevant characteristics (effectiveness, toxicity, user-friendliness, and so on) qualifying for its position relative to alternative therapeutic interventions
Efficiency	A medicine is effective and the balance between therapeutic value and costs is favorable in comparison to other treatments

and, of various alternatives, mebeverine was considered to have the least amount of side effects (34).

The Ministry of Health rejected the advice provided and excluded the drug from the public healthcare package. This decision was challenged both by the medical profession and by the industry and the matter was taken to court. The court concluded that both the Ministry of Health and the industry acknowledged the lack of clear evidence on effectiveness but differ in the opinion whether mebeverine fulfilled the criteria for reimbursement. The court decided that mebeverine should be reimbursed, because the interest in its continued use and funding far outweighed the Ministry's justification for withdrawing the drug from the healthcare package. Following this, the Ministry sought new means to substantiate their claim that mebeverine be removed from the healthcare package and, thus, proposed a new study that could hopefully generate evidence on the drug's lack of effectiveness.

In 1999, this matter was adopted by the department of Department of Policy Analysis on Medicines (PAM) at the HCIB (35). PAM employees performed a policy analysis and wrote a short proposal for the requested trial that was presented in a meeting with the PAM advisory committee. The committee, which consisted of various experts from the field, concluded that a placebo-controlled trial on the effectiveness of mebeverine might not be able to provide the relevant information needed for policy making. Because the Ministry of Health considered dietary advice more efficient, they

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contended that dietary advice should be included in the study. PAM employees then proposed to commission a trial on the therapeutic value of mebeverine compared with dietary advice. However, PAM employees were uncertain about the feasibility of such a trial. In June 1999, they proposed a preliminary study on the feasibility of a clinical trial on the therapeutic value of mebeverine in relation to dietary advice. This preliminary study aimed to assess the possibility of standardizing dietary advice, determine which outcome measures could be considered clinically relevant, and how many patients should be included.

In May 2000, researchers from two departments of general practitioners at university hospitals were commissioned to perform the requested preliminary study. The final report was presented in November 2000. According to the researchers, the major problem was the lack of evidence on the efficacy of any interventions for IBS patients. Evidence from valid controlled trials was needed to develop an evidence-based guideline. The aim of their study was to determine the feasibility of the study. Their study included the identification of an optimal outcome measure; the standardization of dietary advice; and some specific IBS-related problems, such as the inclusion of the relevant spectrum of patients and the identification of subgroups. To get an impression of the effectiveness of usual care, researchers reviewed the literature on dietary advice, held interviews with general practitioners, and conducted an inquiry with patients. To identify objective outcome measures, they reviewed the literature and consulted both general practitioners and internal medicine specialists. They determined that the primary outcome measure should be a global assessment of patient judgment. Additionally, changes in symptoms of patients should be measured. The researchers concluded that standardization of dietary advice would be difficult and discussed which design would be most feasible by referring to criteria for an adequate trial with IBS patients (23). In the end, a trial on the efficacy of mebeverine versus fibers and a placebo was proposed.

Although some questions remained unanswered, PAM employees proposed that a trial on mebeverine be commissioned. Despite this, the advisory committee decided, in January 2001, not to commission another trial on the effectiveness of mebeverine. They contended that the preliminary study failed to reveal (i) the methodological problems of previous trials on mebeverine, and (ii) how these problems could be prevented in subsequent trials. As a result, they considered the feasibility of a methodologically sound trial on the effectiveness of mebeverine to be low due to potential placebo effects and other methodological problems (5).

Perspectives of Policy Makers, Researchers, and Target Populations

As a part of the present study, interviews were held with relevant actors to reconstruct their perspectives. A summary is presented in Table 3.

According to an employee at the Ministry of Health, mebeverine should be removed from the healthcare package because of the lack of evidence on its effectiveness. The Ministry considered alternative interventions, such as dietary advice, to be more efficient. At that time, the Ministry was struggling with increasing costs of drugs and wanted to ensure that ineffective medicines did not impact the medical expenses carried by the community. They claimed that decreasing the cost of drugs was necessary to prevent other problems in health care such as waiting lists. They also claimed that a decision model was useful for deciding which interventions should be reimbursed and which interventions should not.

PAM employees considered an additional placebo-controlled trial on the effectiveness of mebeverine to be useless: ". . . [A]fter a study on the effectiveness, we still might be unable to remove mebeverine from the public health package . . . [Alternatively,] you can try to affect prescription patterns by giving advice. Then, [interventions like] dietary advice and advice on a health regimen become important." To change prescribing patterns, a different kind of information was needed and it was apparent that interventions other that drugs could be relevant. A social scientific approach in research was considered most appropriate. However, given that the pharmacy department at the HCIB is mainly involved in clinical trials, it was unlikely that they would accept a social scientific approach. Consequently, PAM proposed a study on the therapeutic value of mebeverine in comparison to other IBS treatments. Therapeutic value is also a criterion for drug reimbursement of drugs and PAM employees expected that a study on this aspect could provide useful information on prescribing patterns.

According to the researchers, the main problem was a lack of knowledge to support clinical practice. According to the researchers, the first step in the assessment of a drug is to define its efficacy. The effectiveness and therapeutic value of mebeverine could only be deemed relevant in subsequent phases. The researchers contended that dietary advice is very difficult to assess but that, if a diet is effective, this effectiveness is because of an increased fiber intake. Additionally, they claimed that, before the effectiveness of dietary advice can be assessed, knowledge of whether or not fibers actually help was needed; ". . . evaluating dietary interventions is complicated. It is easier to add only a bag of fibres . . . and it is easier to standardise . . .". Researchers assumed that they would get the opportunity to perform the proposed trial.

Physicians acknowledged that mebeverine may not always help patients with IBS and that a placebo effect may be present. Nevertheless, they claimed to prescribe mebeverine because other effective treatments are lacking and because, in some patients, mebeverine appears to be successful. "Mebeverine is easy in use and it is not harmful . . . it is the only therapy that can be given." IBS patients visit general practitioners frequently, but the treatment options are limited. Additionally, patient compliance with alternative interventions, such as dietary advice, is usually low. Thus, the effectiveness of

Table 3. Reconstructed Interpretative Frames of Actors Involved

Actor	Judgement of solution	Problem definition	Background theories	Normative values
Ministry of Health	No evidence on effectiveness mebeverine; exclude mebeverine from health package	Increasing medicines costs	Decreasing costs of medicines is necessary to prevent other problems (waiting lists); decision model adequate for reimbursement decisions	Only effective medicines at the expense of the community; affordable health care
PAM staff	Affect prescribing practice; a study on the effectiveness useless; preferable, research on therapeutic value of mebeverine versus dietary advice	Unlikely that mebeverine can be excluded from the package	For good policy, it is important to know what is important to physicians and patients; a more social scientific approach might experience resistance, because of internal traditions	Research that is relevant and useful for policy making
Researchers	Research on the efficacy of mebeverine compared to fibers is feasible	Evidence on the efficacy of interventions for IBS patients is lacking; previous studies were methodologically flawed	Standardizing diet is complicated; if there's something in diet that is beneficial then these are fibers; valid research provides relevant information	Research that is valid and feasible
General practitioner 1	Mebeverine is effective in some patients; sometimes because the placebo effect; more attention should be paid to psychiatric or mental causes	Some IBS patients visit physicians frequently; no effective treatment strategies available; counseling and reassurance take a lot of time; compliance of dietary advice is low	Etiology of IBS is unknown; frequently, patients are anxious for severe illness (malignancies)	A good relationship with the patient
General practitioner 2	Sometimes medicines are prescribed from discomfort; preferably, advice on healthy lifestyle and healthy food; information flyers from the patients association	Some IBS patients consult general practitioner frequently; not always possible to use other interventions besides medicines	Patients have pain and wonder what the cause might be, including serious diseases; some people are not acquainted with the functioning of their own body; complaints can result from unhealthy lifestyle	Inform and reassure patients
Gastroenterologist	Mebeverine is a standard operating procedure; reassurance is difficult and time consuming; behavior therapy is labor intensive	During consultations, time is limited; patients do have complaints but we do not have a solution for them	Patients sometime expect that a drug is prescribed; IBS is related to anxiety; several subgroups of IBS patients	To spend time meaningfully
Patient	Offer possibility to talk to volunteers with IBS; psychological care useful for listening; mebeverine might be effective in some types of spasms	Physician not enough time for talking and reassuring; too much emphasis on scientific evidence, to less attention to patients experiences	IBS can be due to general increased irritability; diet or stress can lead to complaints; mechanism of IBS is related to the brain–gut axis	Recognition of complaints and disease

PAM, Department of Policy Analysis of Medicines; IBS, irritable bowel syndrome.

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these interventions is variable. According to some general practitioners, IBS is primarily caused by anxiety and not just a physiological abnormality of the colon. However, many patients are not open to psychological explanations of their illness. The presumption of physicians was that patients who receive mebeverine believe that they are taken seriously and will, as a result, visit the physician less frequently. A diagnosis and a prescription for a medicine are important for patients as these actions contribute to a sense of legitimacy and a feeling of recognition. The general practitioner aims to maintain a good relationship with patients and thus prescribes mebeverine. In the words of a gastroenterologist, "I am convinced that if you talk to a patient for a long time, that patient can be helped and will need no medicines. However, that time is lacking."

Patients with IBS mentioned that general practitioners only have a limited understanding of their complaints. For them, recognition of their complaints and being acknowledged is most important. Patients need to accept the existence of their complaints. Therefore, talking about their complaints is important. The patients' association established an IBS helpline that is maintained by volunteers who also have IBS. These volunteer workers can be contacted for answers to questions, advice, or just to tell one's story. According to the patient representatives, mebeverine, is effective in some patients.

DISCUSSION

In this case on mebeverine, there was a lack of agreement on the kind of information that needed to be obtained. There was disagreement on which intervention should be included (diet or fibers) and on which outcome measures were most relevant (a decrease in symptoms, patient satisfaction, or number of consultations). Differences were found with respect to the criteria used to appraise the mebeverine situation. For physicians, establishing and maintaining a good relationship with patients was most important. They consider mebeverine to be helpful in the absence of other interventions. For the Ministry of Health, the increasing cost of drugs was important. It established criteria by which reimbursement decisions should be made and claimed that mebeverine should be excluded due to the lack of evidence needed to fulfill these criteria. In accordance with Hisschemoller's work, we contend that the problem was "ill-structured": actors disagreed on the information needed and the norms at stake (16). Unfortunately, researchers and policy makers did not acknowledge that the problem was ill-structured. As a result, the problem definition shifted during the research project, and the subsequent studies endeavored to answer the wrong question.

The results from the preliminary study did not answer the HCIB's questions. It is important to note that the process of policy analysis can be seen as a series of successive rounds, each with its own problem definition: from initial indication to research problem, from research problem to research questions, and from research questions to the provision of recommendations for policy. In every round, another actor was involved who redefined the problem, based on his or her interpretative frame and the contexts in which he or she worked. The end result is that the findings of the project were hardly useful for policy making. Similar problems have also been found in different settings (18).

The proposed research also did not correspond with the problems perceived by physicians and patients. Physicians did not prescribe mebeverine because they were convinced of its effectiveness. In fact, some physicians acknowledged a relatively high placebo effect in some patients. Physicians claimed to prescribed mebeverine for the following reasons: (i) no other treatment strategies were available, (ii) too little time for counseling was available, and (iii) reassurance and acknowledgment of the patient was important. With this in mind, we can assume that the results of a trial indicating that mebeverine has limited effectiveness would not change physicians' current prescribing practice. Excluding mebeverine from the health package could even limit their treatment options.

The error that was made in this case was that the policy maker failed to analyze the problem from the perspective of the target populations. A trial on mebeverine's effectiveness may have provided a solution to the Ministry's problem and, quite possibly, the evidence would have been sufficient to exclude mebeverine from the health package. However, it would not have solved the physicians' and patients' problems. To dissolve ill-structured problems, adequate problem structuring is essential (16). It is advisable to identify a policy's target populations and involve them during the developmental stages. The objective of involving these groups at an early policy development stage is to assess the degree to which policy implementation is dependent on their cooperation and to also estimate whether the requisite cooperation will be obtained. Obviously, in doing this, policy makers run the risk that policy making will become the prisoner of its target populations. However, when analyses reveal that the requisite cooperation may not be obtained, policy makers can make a choice to apply additional measures so that the requisite cooperation is obtained (13).

To solve the healthcare problem of treating IBS patients, it may be important to acknowledge differences and variances between patients. Although physicians preferred to maintain the option by which they could prescribe mebeverine, it is questionable whether this drug provides the most optimal care for all patients. It is possible that the ambiguity of previous trials can be explained by an implicit assumption that patients groups are homogenous. The physicians we interviewed indicated that what can be considered the most effective treatment is different for different patients. Several theories on the underlying mechanisms of IBS exist. Some contend that complaints are due to physical abnormalities in the colon. Others claim that IBS is a physical expression of psychological factors, such as anxiety. At

the same time, advocates for visceral hypersensitivity, for a neurotransmitter imbalance, and for infection and inflammation exist (20). Despite the varying theories, the previous studies on mebeverine were based on only one mechanism, namely the physical activity in the colon. Obviously, if a case is caused by psychological factors, the use of mebeverine will not eliminate the underlying cause. Patient education and/or behavioral therapy are then considered more appropriate (7;19). Furthermore, it is possible that the total IBS patient population is composed of various subgroups. Unfortunately, professionals have not come to any agreements on the criteria necessary to distinguish between subpopulations (2;22;27;33). In the absence of convincing evidence on specific therapies for identifiable subgroups of patients, physicians are likely required to identify the best treatment for each patient individually. Evidently, this strategy is the current practice of most physicians. It would, however, be advantageous to standardize this process, as standardization can prevent a significant amount of bias. For example, n-of-1-trials can provide objective evidence that an individual patient is truly benefiting from a particular treatment rather than from the nonspecific effects of treatment (29). This approach appears to be promising despite its current lack of application in HTA studies. Additionally, as new drugs for IBS become available (2;9), an approach whereby we identify the best treatment on an individual patient basis becomes important. These new drugs are not as inexpensive or harmless as mebeverine (3), and it is likely that not all patients will benefit from their use. These suggestions correspond with the problems communicated by the physicians and are, thus, likely to be more successful. Furthermore, our suggestions may stimulate increases in mebeverine use among those patients who are most likely to benefit, while decreasing unnecessary prescriptions.

Our study, like all studies, has certain limitations. The first is that only a small number of respondents were interviewed. Although the study aimed to provide insight on the heterogeneity of the stakeholders' perspectives, given the small sample size, it is impossible to draw definitive conclusions on the views of *all* physicians or *all* patients. We cannot precisely gauge the generalizability of our findings. As a result, the recommendations provided with respect to the use of mebeverine among IBS patients are tentative.

CONCLUSION

The analysis of this case indicated that the healthcare problem was ill-structured, which was not acknowledged by the stakeholders involved. As a result, the problem definition shifted and the resulting problem definitions failed to correspond with the problems perceived by the target populations. An argumentative approach in HTAs can help us to identify problems, to uncover the argumentation that underlies these problems, and to develop possible solutions. This, in turn, cannot only make HTAs more relevant to decision makers but also increase the effectiveness of future policy actions.

POLICY IMPLICATIONS

Policy makers should be more acutely aware of the possibility that problems may be defined quite differently by different stakeholders. Problem definitions critically determine the range of solutions that is taken into account. Hence, overlooking incongruencies in problem definition may lead to one-sided, partisan HTAs, with outcomes that are considered valid and relevant by only part of the target population. This, in turn, may severely hamper evidence-based policy making and resolution of the problem. We recommend that policy makers require a cogent analysis of the problem from a variety of perspectives, resulting in evidence of sufficient congruence in problem definition among stakeholders to ensure wider support for HTA outcomes and HTA-based policy decisions.

CONTACT INFORMATION

Margriet Moret-Hartman, MSc (morethartman@hetnet.nl), PhD student, Department of MTA, Radboud University Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; Advisor, Dutch Institute for Healthcare Improvement CBO, P.O. Box 20064, 3502 LB Utrecht, The Netherlands

Gert Jan van der Wilt, PhD (g.vanderwilt@mta.umcn.nl), Professor, Vice Chairman, Department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Center, P.O.Box 9101, 6500 HB Nijmegen, The Netherlands

John Grin, PhD (j.grin@uva.nl), Professor, University of Amsterdam, Netherlands, Scientific Director, Amsterdam School for Social Science Research (ASSR; www.assr.nl), Co-director (for governance studies) of the Dutch Knowledge Network on System Innovations (KSI; www.ksinetwork.nl), Department of Political Science, University of Amsterdam, O.Z. Achterburgwal 237, 1012 DL Amsterdam, The Netherlands

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