Ethics and Evidence in Medical Debates: The Case of Recombinant Activated Factor VII.


Abstract

It is broadly acknowledged that even the most “evidence-based” clinical practice is highly value laden. These values are particular evident in debates about the use of recombinant activated factor VII (rFVIIa)—a drug that is approved only for use in patients with rare clotting abnormalities, but is often used “off-label” to treat major hemorrhage. The debate about whether rFVIIa should be used more broadly for the management of life-threatening bleeding is polarised in spite of stakeholders having access to the same evidence. To understand the disagreement, we conducted a qualitative analysis of the published commentaries surrounding the ‘off-label’ use of rFVIIa. We found that conflicting epistemic and moral values influenced how evidence was interpreted, and contributed to the intransigence of the debate. We conclude that debates about individual therapeutic agents have a moral and political dimension involving competing “prudences” and that new ‘post-normal’ decision-making paradigms are required to resolve such disputes.

Key Words: factor VII; Novoseven; off label; evidence; ethics; post-normal

Introduction

While ethics and evidence-based medicine are often viewed as separate domains of inquiry and practice, what we know influences what we can ethically justify doing, and what we see as our moral obligations shapes the way we interpret evidence. The boundaries between the moral and epistemic spheres become particularly blurred when the health of people is at stake, and even more-so when no ‘officially’ recommended medical intervention is available to help a patient in need. In these instances experts are often obliged to make value-laden judgements about the evidence available to them.

In the case of medicines, clinicians often need to act in the absence of clear-cut evidence of efficacy and safety—in part because of the way drugs are developed. While most basic scientific discoveries still take place in universities, it is the pharmaceutical industry that has the experience, skills, technology and funds to take a new chemical entity from initial discovery through to the clinic. They therefore ultimately have the power to decide what drugs to develop, and for what specific
indications. These decisions depend on a number of factors such as the likelihood that the necessary research can be successfully undertaken to the satisfaction of the regulator, the size of the target population, the price that the drug could sell for on the market, and the period of market exclusivity within which to recoup costs and make a profit.

While in many instances these considerations lead to drugs that are both commercially viable and beneficial to society, at the same time many medical needs remain unmet because there is no commercial incentive to resolve them. To bridge this gap clinicians have one of two options: to enrol patients in experimental trials; or prescribe existing medicines in a new ways, even if these are not consistent with the indications approved by regulatory authorities (i.e. to prescribe medicines “off-label”).

Some off-label uses of medicines are supported by evidence, but in many cases clinicians need to extrapolate from what they know about physiology and pathology and related clinical experience. Off-label prescribing is, therefore, one of the clinical situations in which the boundaries between evidence and values become particularly blurred. The treatment of major hemorrhage using recombinant factor VIIa (rFVIIa) is a case in point.

The rapid growth of rFVIIa for the treatment of uncontrolled bleeding

Uncontrolled bleeding is associated with high mortality, and 30% to 40% of deaths related to trauma are due to bleeding⁷. Mortality associated with intracranial hemorrhage can be as high as 31% at 7 days⁸, and bleeding leads to the death of approximately one third of patients with cirrhosis⁹. Postoperative hemorrhage is also a common complication of cardiac surgery with 2% to 8% of patients who have undergone coronary bypass grafting needing further remedial operations to manage bleeding⁵. There is clearly, therefore, a strong imperative to find better ways to control hemorrhage.

Recombinant factor VIIa (rFVIIa) was originally approved under orphan drug legislation in order to treat the rare condition of haemophilia caused by inhibitors to particular blood clotting proteins. Following reports in the late 1990’s that rFVIIa was successfully used to stop bleeding in gun-shot trauma, there was much excitement about its potential to help patients with uncontrolled bleeding in other clinical settings. As a consequence, off-label prescribing of rFVIIa increased over 140-fold over an 8-year period in the United States, until in 2008, 97% of all uses were off-label⁶. A smaller study published in 2013 showed that all administration of rFVIIa was off-label in two Australian hospitals⁷.

The emergence of new evidence

In recent years, new evidence has emerged about the use of rFVIIa for severe bleeding, which suggests such a high-level of off-label use is unwarranted. Emerging evidence shows that rFVIIa offers no reduction in mortality or severe morbidity⁸ although in some instances it might reduce secondary measures such as use of blood products⁹, hematoma growth¹⁰, and the number of reoperations and transfusions¹¹. Emergent evidence also suggests that concerns about thrombosis as a side effect of rFVIIa are warranted¹². This new information has led to greater scrutiny of the high level of off-label use that had contributed to rFVIIa’s status as a “blockbuster” drug, and resulted in
the publication of a Cochrane review in 2012, which concluded that data supporting the off-label use of rFVIIa was weak, and such uses should only occur within the context of experimental trials.\(^{13}\)

**Responses to new evidence**

In the context of this emergent evidence, one might have expected doctors to stop prescribing rFVIIa for major hemorrhage. A brief review of recent literature on rFVIIa, however, suggested to us that while some clinicians are now adamantly opposed prescribing rFVIIa for massive bleeding, many remain determined to continue this practice. This raises the question: why do clinicians have such variable responses to the same body of evidence?

There are a number of possible (and non mutually-exclusive) explanations for this divergence in attitudes and practices. First, it is possible that some doctors remain committed to off-label use of rFVIIa because of the influence of inappropriate marketing (“off label promotion”) on doctors’ prescribing behaviour. In this regard, it is noteworthy that the manufacturers of rFVIIa settled a case in 2011 for $25 million to ‘resolve civil liability arising from the illegal promotion of … NovoSeven [i.e rFVIIa]’\(^{14}\). Second, ongoing prescribing might stem from the fact that there are physiological reasons for believing that rFVIIa should function as an effective hemostatic agent in many different settings. Third, it is conceivable that the desire to use any agent to prevent or treat life-threatening bleeding—and the associated “rule of rescue”—accounts for at least some continued use\(^{15}\). Fourth, it may be that clinicians simply do not see the existing evidence as relevant to their particular patients, who might have been excluded from clinical research—a common justification for off-label prescribing. Finally, it is possible that the debate about use of rFVIIa is not merely a debate about data, but also a debate about what evidence is, about what should count as evidence, about how evidence should be used in clinical practice, and about how clinical contexts—particularly the desire to act to stop a person bleeding or dying—should influence the way the evidence is used.

All of these possibilities, while plausible, are speculative. To clarify the reasons for divergence in practice, we deconstructed the debate around off label use of rFVIIa, and characterised its main conceptual features and tensions. We did not seek to provide a normative analysis as to whether or not the evidence supports the case for off label prescribing. Nor did we try to provide a historical analysis of how attitudes and clinical practice have changed. Rather, we sought to make visible the moral and epistemic values underpinning stakeholders’ opinions and practices. On the basis of our analysis, which is described in this article, we suggest that debates such as those surrounding rFVIIa will not be resolved simply by conducting more studies, and that, therefore, there is (also) a need for conceptual and procedural frameworks that more systematically incorporate values into clinical policymaking.

**Methodology**

We performed a qualitative empirical analysis of the debate surrounding the use of rFVIIa for management of uncontrolled bleeding. A Pubmed search was performed on 5 October 2012 using the search terms: recombinant FVIIa; Novoseven; recombinant factor VII; and recombinant activated factor VII. Since our research was concerned with the views of stakeholders rather than the evidence for or against the use of rFVIIa, the search results were limited to articles types ‘comments’ and ‘editorials’ to capture relevant editorials, opinion pieces, commentaries and letters to the editor in
the medical literature. The search included papers published between November 1999, when the first published report of successful off-label use of rFVIIa was reported, and October 2012. The search was limited to the English language.

In total 130 separate articles from 60 different journals were identified. The greatest number of articles were published in the *Journal of Thrombosis and Haemostasis* (18 articles), the *New England Journal of Medicine* (14 articles), *Neurology* (9 articles), the *British Journal of Anaesthesia* (6 articles), the *Annals of Thoracic Surgery* (5 articles), the *Journal of Trauma* (5 articles), *Anaesthesia* (5 articles), *Anaesthesiology* (5 articles), and the *Canadian Journal of Anaesthesia* (5 Articles).

We drew both on Morse’s outline of the cognitive basis of qualitative research16 and on Charmaz’s outline of data analysis in grounded theory17. This procedure involved initial coding via line-by-line analysis and synthesizing codes into categories until no new codes could be developed from the data. A coding tree was generated. Throughout the data analysis, a process of constant comparison was employed to refine, enrich, and reorganise the emergent themes and categories. Thematic saturation was reached after approximately 30 articles (that is, no new themes emerged after 30 articles had been analysed). The categories were then examined in light of a theory of ‘competing prudences’ that we had developed in other work on off-label prescribing18. This framework requires the identification of moral priorities, epistemic standards, and attitudes towards uncertainties expressed in the published opinions of stakeholders to determine, in broad terms, the trade-offs stakeholders make between these factors when faced with uncertainty. Because this was a qualitative analysis, rather than a systematic review, we did not attempt to enumerate the findings. Rather, we sought to apply, and enrich, our theory of ‘competing prudences’.

**Results**

**Values and evidence in debates about rFVIIa**

According to the tenets of evidence-based medicine, one might expect the debate about off-label use of rFVIIa to be characterised simply by a number of questions: does the intervention harm the patient, does the intervention benefit the patient, and is the intervention appropriate? The last question can be further divided into concerns about whether the intervention is cost-effective, whether it is more beneficial than harmful, and whether it is more effective than alternative treatments available. In the absence of scientific or clinical consensus regarding the answers to these questions our findings reveal that participants in the rFVIIa debate argued for or against off-label prescribing on the basis of a number of different moral and epistemic priorities.

Three primary moral principles were invoked throughout the debate, namely beneficence, non-maleficence and social justice. With regards to beneficence, some stakeholders emphasised the therapeutic challenge faced by clinicians treating major hemorrhage, which some characterised as a battle that requires as many weapons and manoeuvres as possible19. The very high mortality associated with massive bleeding was seen to increase the moral imperative to act, and added to the frustration at the lack of options available20.

On the other hand, concerns about non-maleficence (avoiding harms from rFVIIa) were apparent in warnings proffered by some commentators and in their calls for caution21. Perhaps most prominent amongst those advocating for a cautious approach was Aledort who soon after the earliest report of
off-label use of rFVIIa in 1999, warned against ‘extrapolating case reports to general clinical practice’ until the medical community understood the potential for harm from thrombosis\textsuperscript{22}—a position that Aledort has maintained since this time\textsuperscript{23}.

Appeals to social justice were apparent in concerns about the cost of treatment, and the need to ensure cost-effectiveness and comparative effectiveness to increase the intervention’s value to society\textsuperscript{24}. Perhaps the strongest statement emphasising both non-maleficence and social justice were apparent in the statement of Avorn and colleagues published in 2011, 12 years after rFVIIa started to be used off-label\textsuperscript{25}:

“So here we have a rapidly increasing use of a treatment that does not benefit patients and increases the risk for dangerous thrombotic events – and which the investigators estimate to cost $10,000 per dose. Allowing physician autonomy… is appealing, but not when it results in unhelpful, dangerous, and costly decisions”.

In contrast, while other commentators acknowledged the enormous costs of rFVIIa, they denied that this provided sufficient justification for rationing on the grounds that beneficence, rather than justice, should be the principal driver of practice:

“…we can expect continued resistance to rhFVIIa use from the blood bankers and pharmacists who often act as its fiscal gatekeepers but never have to give bad news to a patient’s family”\textsuperscript{26}.

Commentaries regarding the off-label prescribing of rFVIIa also varied enormously in their construction and use of knowledge. Some stakeholders emphasised their personal experiences with rFVIIa and the number of positive case reports published\textsuperscript{27}. Others emphasised the physiological rationale for using rFVIIa to treat bleeding in any context\textsuperscript{28}, while others were sceptical of the validity of clinical anecdotes, case reports and mechanistic accounts, and emphasised the necessity for practice to be based upon high level analyses, particularly randomised controlled trials\textsuperscript{30-29}. For instance, Yank and Stafford stated that there was no convincing epidemiological evidence of rFVIIa’s efficacy, leading them to:

“…strongly caution against such wide adoption of off-label therapeutics without convincing evidence of efficacy and adequate studies of harm.”\textsuperscript{30}

Our analysis revealed that positions regarding the off-label use of rFVIIa can be understood in terms of the weight given simultaneously to different moral principles and forms of evidence. These different approaches can be understood as two different forms of clinical prudence, which we have called “active prudence” and “precautionary prudence”.

**Active Prudence**

What we call “active prudence” is motivated by the need to confront and respond to the immediate needs of patients. It therefore prioritises beneficence, is focused on action rather than reflection, and is epistemologically pragmatic rather than idealistic. When little definitive evidence exists about an intervention’s benefits or harms active prudence accepts that clinicians must rely on their clinical judgement and personal experiences. This is especially the case when high-grade evidence is unlikely
to ever be generated due to practical difficulties with the research process. For instance in the context of management of post-partum hemorrhage, Ahonen and Jokela state:

“...we need randomized controlled trials to determine whether rFVIIa is effective, but these studies are unlikely to be implemented in the setting of unanticipated PPH... In 2003, we started to use rFVIIa in life-threatening PPH. With growing experience we started to use it to avoid hysterectomy.”

Hauser and colleagues also illustrate an attitude consistent with active prudence when they bemoan the fact that the FDA would not approve rFVIIa for trauma because the CONTROL trial (a phase 3 RCT) could only demonstrate decreased blood loss, and not mortality benefit. They contend that the FDA is being contradictory for requiring ever-higher evidence standards while simultaneously applying more restrictive ethical standards on research. In an environment where the clinical problems that remain are becoming more difficult to solve, they argue this makes it all but impossible to generate ‘strong’ evidence.

Active prudence is also characterised by the willingness to act in the face of uncertainty about harms. What is known is given priority over that which is unknown, or might never be known. For instance, although generally resistant to the idea of rFVIIa’s broad use for management of bleeding, Levi agrees that when faced with serious need, existing evidence and knowledge must be given priority regardless of how limited it may be:

“...in such a catastrophic situation a potential, though uncertain, beneficial effect of recombinant FVIIa would weigh more strongly against unknown or theoretical safety issues.”

Roberts perhaps expresses the strongest version of active prudence by dismissing questions that do not address a patient’s immediate welfare as hypothetical and irrelevant. And even if the results of harm are true ‘this risk is likely dwarfed by the risk of allowing blood loss to continue unabated’.

Hayanga argued that off-label use of rFVIIa is likely to not only continue but also increase in the absence of any ‘evaluative data’ due to positive results from anecdotal reports.

Precautionary Prudence

The position that we refer to as “precautionary prudence”, in contrast, is characterised by a commitment to non-maleficence and/or social justice even if some demonstrated or hypothetical benefit must be sacrificed. A strong commitment to these moral principles is associated, in turn, with a sceptical view of claims of effectiveness that are not based on high levels of evidence according to the EBM hierarchy. Rather than responding to immediate clinical needs, those who espouse precautionary prudence prioritise the qualities of reflection and avoidance. For example, in his argument against the use of rFVIIa as a general haemostatic agent, Levi expresses his view that case studies and series are not a valid source of evidence and that what is needed is a “scientific” approach:

“...we should never be blinded by our and others’ successes in individual cases and, even in case of a very appealing new pharmaceutical agent, adhere to the well-founded...
principles of creating a scientific basis for pharmacological treatment efficacy and safety.”

Levi also warns those who support rFVIIa’s use about many previous cases in the medical literature where new interventions had initial spectacular effects that were ‘later found to be based on coincidence, bias, or other confounding factors’, and therefore believes that clinical ‘logic’ is not reliable (p. 1696). Detry and colleagues likewise state that conclusions about rFVIIa use for the prevention and treatment of excessive bleeding cannot be made because there is no ‘sufficient scientific data ... about the efficacy and cost-effectiveness’.

The ideal source of evidence for those who adhere to precautionary prudence are randomised controlled trials. Conclusions based on ‘weaker’ sources of evidence are considered to be only hypotheses that need to be interpreted with caution. For instance, while Hill and Subramanium believed that rFVIIa may cause unexpected posthemorrhagic hydrocephalus they were willing to concede that this is only a hypothesis and a randomised controlled trial is needed to test it:

“We await data from the current FAST trial, a phase 3 randomised trial of factor VIIa for acute ICH to either affirm or refute our hypothesis.”

Those who promoted precautionary prudence also tended to be more concerned with the possibility that data on rFVIIa was biased, and that clinical trials and their reporting had been contaminated by funding from Novo Nordisk. They argued that, even where there was evidence to support off-label use of rFVIIa, this may be because ‘drug companies are ... skilled in getting the results they want from clinical trials’.

Attribution of Meaning to Evidence

The critical responses to the study published by Levi and colleagues, which reported strong evidence of harm associated with the off-label use of rFVIIa, provides further illustration of the two versions of prudence. In response to the publication of this study, some stakeholders took an active prudential position, and defended the off-label use of rFVIIa against emerging evidence of non-benefit and harm. Patel and colleagues, for example, attacked the methodology of the study to undermine its value:

“Pooling of groups of patients with different thrombotic and bleeding risks ... does not assist in clinical risk–benefit decisions, since it seems evident that such patients should be treated differently.”

Arelano-Rodrigo also questioned the results by arguing that the method of analysis did not compare rates of death from any cause against thromboembolic events, and therefore were not clinically relevant.

In contrast, Yank and Stafford argued that the risk-benefit profile was indeed known and that there was no convincing evidence of efficacy, and that, therefore, any evidence of harm had to be taken seriously. This view was supported in a Nature Medicine editorial in which it was argued that evidence of health risks associated with off-label use was ‘compelling’ and ‘worrisome’, and that in some cases rFVIIa was being ‘abused’. Combined with evidence of the high rate of off-label use, it
was argued that the case of rFVIIa ‘raises questions as to how to properly regulate off-label drug use’.

Avorn and Kesselheim also argued that the rapidly increasing use of an expensive drug ‘that does not benefit patients and increases the risk for dangerous thrombotic events’ is not only unwarranted and driven by commercial rather than clinical factors, but also created the possibility of claims against doctors in negligence. In support of active prudence, Karkouti and Levy responded that ‘comments on off-label use of rFVIIa that do not consider the clinical context in which the drug is being used may be flawed’, and that the published evidence about risks ‘is probably dwarfed by the risk for allowing blood loss to continue unabated’.

These responses to evidence illustrate that those who have a commitment to a particular form of prudence will interpret new evidence in accordance with their prudential perspective (Figure 1).

**Discursive Practice**

**Discussion**

The debate we have analysed shows that evidence alone cannot resolve the debate about off-label use of rFVIIa, and may never be able to do so. Even if further high quality research into rFVIIa can be conducted, its conclusions will likely be contested. Not everyone will agree that a particular method and the subsequent results lead to the conclusions the author claims. Even the results of randomized clinical trials may be challenged in terms of their inclusion and exclusion criteria, generalisability, therapeutic regimen, control group, and subgroup analysis. The selection of endpoints of the studies may also be contested—particularly whether mortality is the only relevant outcome, or whether clinically relevant morbidities or surrogate outcomes such as transfusion requirements, blood loss, re-operative rate or haematoma size are sufficient.

Under circumstances where conflicting values exist alongside contested evidence we suggest that stakeholders adopt different prudential stances in response to clinical and evidential uncertainty. This challenge to the idea that responses are purely ‘rational’ aligns with the views of the legal
scholar Ronald J. Allen who argues that rationality is a ‘multivariate search for tools to understand and regulate a hostile environment’48, and the view of the moral philosopher Shafer-Landau who sees rationality as a derivative of values:

‘...exercising one’s rationality essentially involves a series of operations over one’s existing commitments... Being rational is a matter of enacting particular kinds of reasoning process that have their origin in a set of commitments that are not themselves rationally assessable.’ (p. 100).

The fact that different prudential principles are not openly declared, but instead cloaked in terms of scientific or clinical disagreement, is consistent with Gallie’s observation that while stakeholders might be committed to conflicting preferences and values, they are nevertheless all able to put forward perfectly rational reasons for their differing positions49. Gallie’s work can also help to explain why it is so difficult to resolve these kinds of debates. Incommensurable disagreements arise, according to Gallie, because there is no objective way to judge one form of rationality better than another. Levi also seemed to recognize this and argued that disagreements can only be resolved as long as those disagreeing between themselves identify ‘their shared agreements in full beliefs, probability judgments, and value judgments’50. If such common ground does not exist there are no grounds for resolution.

The need for the tools of “post-normal science” to mediate between conflicting prudences.

It is, of course, important that research into the efficacy, safety and cost-effectiveness of rFVIIa continues, and that its use in practice is carefully monitored. But even this is unlikely to resolve the dispute entirely. In contexts such as these, where there is not likely to be a purely scientific or rational resolution to a debate about scientific evidence, a new mode of problem solving is required. The phrase ‘post-normal science’ has been used to capture the fact that science is unable to address problems where ‘facts are uncertain, values in dispute, stakes high and decisions urgent’51. Scholars of post-normal science have recognized that many modern problems are irreducibly complex, and argued that solving them requires ‘new methods ... to make our ignorance usable’(p. 290).

Hauser and colleagues implicitly invoke the principles of post-normal science in their criticism of the FDA’s rejection of evidence about rFVIIa’s benefit for trauma patients, which is the off-label indication with the strongest evidentiary support, they state:

“...the holdings of the FDA with respect to acute care research have made acute trauma research in the United States all but impossible... [now that] the “low-hanging fruit” of clinical trauma research is now simply gone.”52

Compare this to the statement of Farrell writing about the ‘wicked’ problems post-normal science is meant to address:

“...in late-industrial societies (that is to say, in the so-called West) straightforward planning problems have all been more or less solved and the ones still remaining unsolved are “wicked” – persistent, complex, and difficult or perhaps even impossible to solve”53.
According to theorists of post-normal science the way to approach these problems is not to aim for complete uniformity of practice, but also not to leave decisions only to individual clinicians or hospitals making purely ad-hoc decisions (as is currently the case). Rather, the goal is to find a “middle ground” by extending the quality control function of peer review beyond experts by incorporating the views of others in the community. In the case of rFVIIa for off-label uses, we argue that this effectively means that the form of prudence chosen, whether active or precautionary, must align with the community’s fears and hopes, appetite for uncertainty, and willingness to trade-off risks for benefits.

In this case, the “community” might consist of the clinical policymakers who already make decisions about clinical practice guidelines, as well as practicing clinicians (i.e. those at the “front line” dealing with bleeding patients), public or private insurers and payers (depending on the health system), and members of the public. The size of these communities would depend on the kind of health system in place. In the United States, for example (at least for the time being), it is likely that the boundaries of health insurance companies would determine the size of the relevant communities, while in countries like Australia, with national formularies, the relevant “community” would be much larger. This raises the question of how to make sure that patients and members of the public (i.e. “consumers” of medicines such as rFVIIa) have a voice in such communal processes.

**Involving consumers in Decision Making Process**

Jurgen Habermas argued that the only moral norms that would enable resolution of disagreements were those that were agreed to by all those affected by the application of it. We agree with this principle in general but believe that in practice it has certain serious limitations. First, is the problem of defining those affected; second, is the fact that not all those affected are impacted in the same way, or to the same degree; and third, is that it is not clear what method could be used to include all those affected in the decision making process.

We believe that citizens’ juries provide a practical, although imperfect, application of Habermas’ principle, and a useful means of ensuring that consumers have a voice in “post-normal” science. This approach was advocated by the health economist, the late Gavin Mooney, who argued that the distribution of limited health care resources should be guided by the community, rather than be limited to economic evaluations and the views of a few powerful individuals or institutions. Mooney states the problem in the following way:

“…until it is known what the good of health care is there cannot be a judgment about what is better, and ... until it is known what is better there cannot be a judgment about what is quality... there is no-one better placed to do this than the community.”

The need for such an approach to resolving the debate about off-label use of rFVIIa becomes all the more acute in a context where many believe that commercial interests have had an undue influence over off-label prescribing patterns.

While a citizen’s jury will not necessarily be able to interpret the significance of technical evidence presented to them, information can meaningfully be sought about ways of addressing uncertainties and trading off costs and benefits, and benefits and harms. It is, after all, the perception of
uncertainty that led to the intransigence of the disputants in the first place, and trade-offs are essentially value judgments, which cannot be reduced to technicalities.

For this to work, uncertainties would have to be elaborated and made explicit to participants in the decision making process in order to expose them ‘to the fundamentally political nature of the final decisions at which they arrive’58. How this might be done is beyond the scope of this paper. However, some thoughts on how statistical evidence might be presented ‘innocently’ so that it may be better interpreted by juries are presented by Ligertwood and Edmond59. They argue that evidence needs to not only be relayed accurately but also in a way that conforms to ‘lay capabilities’, since statistical reasoning is not necessarily intuitive or natural. Frameworks for clarifying and communicating uncertainties have been developed, for instance the NUSAP system developed by Funtaowicz and Ravetz to alert people to the fact that statistical work has a social dimension, and to make apparent the ‘meaningfulness’ and quality of numerical expressions60.

It must be realized that none of these processes or frameworks guarantee a resolution to debates such as that surrounding off-label prescribing of rFVIIa. But they do make explicit the moral and political dimensions of science and medicine. And this, in turn, reminds us that these debates—even about individual therapeutic agents such as rFVIIa—are ultimately about what we, as a society, want from our health system and how health care can be democratized so that citizens can participate in decision-making.

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