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Sins and Risks in Underreporting Suspected Adverse Drug Reactions

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Abstract

The underreporting of suspected adverse drug reactions remains a primary issue for contemporary post-market drug surveillance or pharmacovigilance. Pharmacovigilance pioneer W.H.W. Inman argued that "deadly sins" committed by clinicians are to blame for underreporting. Of these "sins," *ignorance* and *lethargy* are the most obvious and impactful in causing underreporting. However, recent analyses show that *diffidence, insecurity,* and *indifference* additionally play a major role. I aim to augment our understanding of diffidence, insecurity, and indifference by arguing that these sins are underwritten by value judgments arising via epistemic risk. I contend that "evidence-based" medicine codifies these sins.

1. Introduction

The underreporting of suspected adverse drug reactions (SADRs) remains a significant problem for post-market drug surveillance or pharmacovigilance. Estimates suggest that 90–95 percent of SADRs go unreported to regulatory bodies and databases (Hazell and Shakir 2006; Lopez-Gonzalez, Herdeiro, and Figuerias 2009; Hohl et al. 2018). Since these reports form the foundations of pharmacovigilance research, the problem of underreporting is a major hindrance to pharmacovigilance's aim of monitoring the safety of drugs. Researchers often group the causes of underreporting into a scheme first proposed in the 1970s by pharmaco-epidemiologist and pharmacovigilance pioneer W.H.W. Inman. Inman's "deadly sins" are clinicians' attitudes or influences that prevent SADR reporting (Inman 1976). Inman and other researchers have articulated the "sins" of *complacency,* in that only safe drugs are allowed on the market; *fear* of litigation; *guilt* at having harmed a patient; *ambition* to amass and publish case reports; *ignorance* of knowing how to report; *lethargy* in reporting; *indifference,* not believing that a single SADR matters in the grand scheme of medical knowledge; *insecurity* in positing some adverse event as an SADR, and *diffidence* at "mere speculation" of cause–effect relations in clinical observations (Inman 1976; Inman and Weber 1986; Lopez-Gonzalez, Herdeiro, and Figuerias 2009; Palleria et al. 2013). Ignorance and lethargy are taken to be the most impactful of these sins but close behind in their impact are insecurity, diffidence, and indifference (Lopez-Gonzalez, Herdeiro, and Figuerias 2009; García-Abeijon et al. 2023). Therefore, interventions aimed

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at mitigating underreporting that fail to address insecurity, diffidence, and indifference—in addition to lethargy and ignorance—will likely be ineffective.

This paper has three aims. Firstly, I aim to augment our understanding of insecurity, diffidence, and indifference by arguing that they are consequences of values held in response to epistemic risk or, broadly, "the risk of being wrong." When there is epistemic risk, value judgments guide action. I will show that insecurity, diffidence, and indifference are underwritten by aversions to anecdotal evidence. I do not doubt the other sins can also be construed as consequences of value judgments in epistemically risky circumstances. However, I focus only on insecurity, diffidence, and indifference here because of their impact on underreporting and for the sake of conciseness.

Second, I contend that the roots of these aversions are at least codified by normative commitments to "good" evidence in "evidence-based" medicine (EBM), including an overarching disvaluing of anecdote. This is evident when looking at EBM guidelines, such as the *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice,* which states that control variables are needed to posit some phenomenon as an SADR (Guyatt et al. 2015). Philosophers of medicine have already highlighted issues with drug-safety monitoring and EBM (for example, Osimani 2014; Stegenga 2016). I simply aim to connect similar concerns with the sins in mind. Note that I am not placing the blame for the sins wholly on EBM, as Inman articulated them more than a decade before EBM's entrenchment in the 1990s. Nor am I positing that mitigating the sins alone solves under-reporting. The sins are only one component—albeit a significant one—of underreporting, as institutional features that individual clinicians have no control over also contribute to underreporting (Hohl et al. 2018).

Third, I aim to show how the epistemic risk framework adds nuance to a common mantra of pharmacovigilance regarding the problem of underreporting: "when in doubt, report." The analysis here shines a light on what this "doubt" is composed of, which can help pharmacovigilance educators pinpoint and further articulate steps toward mitigating underreporting. It also reckons with the possibility of *over*reporting. Given the scope and magnitude of the problem of underreporting, simply articulating the problem in an epistemological framework may be of value to those actively seeking and working toward solutions.

In arguing these three points, it is first necessary to give a brief background on the problem of underreporting, which follows in section 2, and a brief background on the epistemic risks and values framework, which follows in section 3. Section 4 then explains how insecurity, diffidence, and indifference are caused by values and aversions in response to epistemic risk and uncertainty. Section 5 contends that EBM's hierarchical view of evidence at least codifies or entrenches the values underlying our three sins of note. I explain how the epistemic risk framework adds nuance to "when in doubt, report" and consider the possibility of overreporting in section 6, thereafter concluding and highlighting some limitations to the analysis in section 7.

2. The Necessity of Pharmacovigilance, the Problem of Under-Reporting, and the Deadly Sins

The history and development of drug monitoring is closely tied to the history of public health tragedies and controversies.[1] The organization that would eventually become the US Food and Drug Administration (FDA) arose in 1906 in response to concerns about the safety and misbranding of medicines containing heroin, alcohol, and cocaine. The 1938 Federal Food, Drug and Cosmetic Act endowed the FDA with the power to reject market access to medicines, spurred on by the sulfanilamide disaster, when an estimated 107 deaths were caused by an ingredient in sulfanilamide products that was similar to antifreeze (Ballentine 1981; Carpenter 2010). The 1962 Kefauver-Harris Amendments, which added proof of effectiveness and demonstrated safety to the premarket requirements of new drugs, was spurred on by the thalidomide disaster, when thalidomide was prescribed in the late 1950s and early 1960s as an anti-nausea treatment for pregnant women but caused birth defects in an estimated 10,000 children worldwide (Kim and Scialli 2011).

More than six decades later, the need for pharmacovigilance remains paramount, especially considering recent disasters and controversies, such as rofecoxib (Wadman 2005), oxycodone (Van Zee 2009), and aducanumab (Brockmann et al. 2023), among others. Well over 100,000 people die each year in the US from adverse drug reactions, many thought to be preventable (Light, Lexchin, and Darrow 2013). Adverse drug reactions are estimated to be in the top five leading causes of death in hospital settings in the US (García-Abeijon et al. 2023). However, we are often unaware of a drug's possible adverse reactions until it has been on the market and used by a large population (Onakpoya, Heneghan, and Aronson 2016). To detect a 1-in-10,000 occurring adverse reaction or side effect of some novel drug,[2] a 95 percent power detection method requires 30,000 patients to have taken that novel drug (Naina-Mohamed 2014). Most clinical trials are simply not that big. And, this problem of detection is compounded when we add the ubiquitous considerations of comorbidity and poly-pharmacy.

So, in order to determine the adverse reactions of some drug, we require what pharmacovigilance researchers call "spontaneous reports," or reports of SADRs of drugs that are on the market. The FDA began soliciting and collecting these spontaneous reports in 1969 in the wake of thalidomide and, later, diethylstilbestrol, a synthetic form of estrogen given to pregnant women to prevent pregnancy-related complications, which had a teratogenic adverse effect of cancer (Herbst, Ulfelder, and Poskanzer 1971). The FDA continues to collect SADR reports through online resources such as MedWatch and the FDA Adverse Event Reporting System (FAERS). In the US, patients can report their SADRs to the FDA as well, something that many patients likely do not know.[3] Similar databases exist in other countries and, through the World Health Organization (WHO) and nongovernment reporting, services such as RxISK.org also exist. When enough SADRs are collected about

[1] However, it would not be right to say that these tragedies and controversies themselves alone caused regulatory action—debates on regulatory action were already ongoing in the cases of the 1906 Pure Food and Drugs Act, the 1938 Federal Food, Drug and Cosmetic Act, and the 1962 Kefauver-Harris Amendments (Carpenter 2010).
[2] "Side effects" and "adverse reactions" are, strictly speaking, different phenomena, though they are often used interchangeably in medical research (Due 2023). For the purposes of this paper, I assume the side effects of interest are those that are explicitly negative; that is, adverse, unless stated otherwise. I also use "adverse event" or "adverse phenomenon" to refer to cases where the event or experience of the patient is not causally related to the medical intervention.
[3] https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting.

some drug and some effect is determined as significant by regulators, investigations begin that may not otherwise have been carried out. For this reason, spontaneous reporting is often touted as the "cornerstone" of pharmacovigilance (Moore 2014). Spontaneous reporting has successfully resulted in the removal of dangerous drugs from the market, including fenfluramine, terfenadine, mibefradil, bromfenac, astemizole, grepafloxacin hydrochloride, and cerivastatin sodium, and has led to increased regulation on drugs such as isotretinoin, clozapine, and fentanyl, among others (Wysowski and Swartz 2005).

However, it is estimated that up to 95 percent of SADRs go unreported to regulatory bodies and databases (Hazell and Shakir 2006), a figure readily assumed in pharmacovigilance research.[4] This constitutes the problem of underreporting. Underreporting means that data that would potentially save lives, money, and time goes unused, and is a barrier to the process of discovering side effects. Underreporting is caused at an institutional level (Hohl et al. 2018) insofar as medical practice is just not designed to maximize the aims of pharmacovigilance, but it is also thought to be caused because of clinician and healthcare provider inaction as well, or at least is so posited by Inman's "deadly sins." As outlined above, Inman's secular sins and their recent amendments are the following attitudes that prevent reporting SADRs:

- *complacency* is the sin of believing only safe drugs are allowed on the market, so whatever adverse event a patient is experiencing is not an SADR;
- *fear* is the sin of not wanting to admit having done harm and opening oneself up for litigation;
- *guilt* is the sin of feeling ashamed of having harmed a patient and wanting to move on and forget it happened;
- *ambition* is the sin of wanting to amass reports and publish them, serving oneself while preventing the data from being immediately available to pharmacovigilance researchers;
- *ignorance* is simply the sin of not knowing how to report or even that reporting is a possibility;
- *lethargy* is the sin of failing to prioritize reporting;
- *indifference* is the sin of not believing a single SADR matters for pharmacovigilance research;
- *insecurity* is the sin of hesitation to posit some adverse phenomenon as an SADR; and
- *diffidence* is the sin of fearing to appear foolish at "mere speculation" of cause–effect relations from single cases of clinical observation (Inman 1976; Inman and Weber 1986; Lopez-Gonzalez, Herdeiro, and Figuerias 2009; Palleria et al. 2013).[5]

Mitigating underreporting means mitigating the sins; doing so is a primary goal for pharmacovigilance.

A 2009 review of empirical data on underreporting by Elena Lopez-Gonzalez and colleagues found that ignorance was responsible, or played some role, in 95 percent of cases of failed reporting, followed by lethargy at 72 percent of examined cases. A 2023 update of this review, by some members of the same team, found that ignorance and lethargy remain at the forefront of the sins responsible for underreporting (García-Abeijon et al. 2023).

[4] The Hazell and Shakir (2006) paper has been cited more than 2,000 times, at least as of March 2024.
[5] We might also think of these sins as something like "epistemic vices," or ways of thinking that impair an agent's capacity to be a good investigator, or respond to demands of inquiry (Kidd 2018).

However, the 2009 review also found that diffidence, indifference, and insecurity play a role in at least 67 percent of examined cases. The 2023 review found that complacency regarding the safety of drugs on the market has risen—a subject deserving of its own analysis—and that indifference, insecurity, and diffidence had fallen in their suspected impact, to 27.7 percent, 33.8 percent, and 44.6 percent, respectively. Even if something like indifference is only responsible for one of every four cases of reporting failure, it still warrants examination. Moreover, as stated above, the other sins are likely explicable in terms of the following analysis. Regardless, what one can see from these reviews is that simply educating clinicians and healthcare providers by telling them how to report is an incomplete solution to underreporting. A substantial amount of underreporting occurs even when health professionals are aware of reporting. Better solutions to underreporting will be those that go beyond addressing ignorance and lethargy, including things like insecurity, indifference, and diffidence. Articulating and augmenting our understanding of these in epistemological terms is the subject of the next section.

3. Epistemic Risk and Values

Values play a major role in scientific practice. Whether they should, and to what degree, is an ongoing conversation in the philosophy of science (for example, Betz 2013; Holman and Wilholt 2022), which is beyond the scope of this paper. Discussions about values tend to focus on the role they play. Philosophers' accounts range from how values are related to evidence and standards of evidence (Douglas 2000), community standards (Wilholt 2009), and adjudication (Biddle 2013; Hicks 2014). A common theme is that values become problematic when they negatively affect or constrain epistemic progress (Steel 2017), which can only be determined case by case (Longino 1996). Many contemporary discussions about values find their roots in Heather Douglas's (2000) account of how values play a role in data characterization and standards of evidence.[6] Douglas discusses a trial determining whether a particular toxin caused tumors in animal subjects. Establishing whether the suspected tumors were caused by the toxin was ambiguous; that is, there was a risk of inferring a false positive (the toxin was wrongly ascribed as tumor-causing), or a false negative (the toxin was wrongly ascribed as not tumor-causing). This risk of inferring a hypothesis that is a false positive or a false negative is what Douglas calls an "inductive" risk. In such cases, non-epistemic values such as "safety" may have a legitimate role in decisions. The harms that might arise from allowing the toxin market access if it did cause the tumors outweighs the harms that would arise from not allowing the toxin on the market if it did not. Therefore, in such a circumstance we might *prefer* erring via false positives; that is, being *averse* to erring via false negatives. These preferences and aversions can be caused by external factors—if I have a conflict of interest and am being paid by the private company that owns the toxin, I might interpret the toxin as not tumor-causing; if I am being precautionary, I may interpret the toxin as tumor-causing. In other words, given the inductive risk of accepting or rejecting a hypothesis about the toxin's safety, non-epistemic preferences and aversions play a role—implicitly or explicitly—in the choice.

[6] It is worth mentioning that work on values and inductive risk dates back to the 1950s and 1960s with work by Rudner (1953), Hempel (1965), and others.

This inductive risk of hypothesis acceptance is a subset of a more general type of risk: *epistemic* risk; that is, the risk of being wrong. Justin Biddle and Quill Kukla (writing as Rebecca Kukla) (2017) highlight that within epistemic risk, a variety of risks exist. Related to inductive risk is *phronetic* risk, or a risk about what counts as data, or what aspects of a phenomenon are data in the first place.[7] Biddle and Kukla illustrate this with an example of a radiologist examining image planes: "A radiologist does not see an MRI … the same way a layperson does … when she sees an abnormal growth or whatever it may be, her vision already encodes a balancing of values; if her perception is extra-sensitive to abnormalities, it will catch more false positives and fewer false negatives" (2017, 221). Given a risk or ambiguity about some phenomenon as an abnormality, preferences and aversions play roles in determining some phenomenon one way or the other. If we imagined a pair of radiologists looking at a slide with some ambiguous phenomenon and they differed on whether the image constituted an abnormality, it would likely be because of different values considering phronetic risk. For example, one may be concerned with complications from overdiagnosis, the other from underdiagnosis (Biddle 2016). In other words, when there are epistemic risks—risks of being wrong—values arise and guide action.

What makes a case of values playing a role in decisions, good or bad, is typically whether the value in question is impacting the epistemic progress or aims. Some value such as "simplicity" might better achieve some epistemic goal of communication or understanding even if it idealizes content. Values such as "profit-maximizing" can negatively affect epistemic aims like drug effectiveness (Biddle 2007; Hicks 2014). In cases where values are clearly negatively affecting epistemic aims, we ought to change or rebalance those values. In short, when there are uncertainties and risks, non-epistemic values arise. These values guide actions and decisions in ambiguous circumstances, whether licensing a hypothesis given vague data, or even determining what counts as data in the first place. If there is rampant over-acceptance of some hypothesis or overdiagnosis of some condition going on, bad values are likely a key culprit and must be a target of change. The next section shows how this is mirrored in the sins of indifference, insecurity, and diffidence.

4. Insecurity, Indifference, and Diffidence as Aversions

Let us start with insecurity. Insecurity was not originally proposed by Inman but has since found its way into the list of sins (Lopez-Gonzalez, Herdeiro, and Figuerias 2009). Insecurity is the sin of encountering an ambiguous adverse patient experience and, based on that ambiguity, failing to see it as an SADR. The "insecure" clinician sees the ambiguous event and concludes that it is not an SADR at all, leading to a failure to report. What is going on here is analogous to the radiologist case above. As with the radiologist, there is genuine ambiguity in how to classify some perceived phenomenon. In the case of insecurity, there is an *aversion* to seeing the ambiguous adverse phenomenon as a possible SADR. In other words, insecurity arises as an aversion—a value judgment—as a result of epistemic risk. *Not* committing the sin of insecurity would be to see the ambiguous event as an SADR.

The sin of indifference describes cases unlike insecurity insofar as a clinician acknowledges that some phenomenon is an SADR. However, there is still a failure to report

[7] This is something Douglas (2000) also takes into account in discussing inductive risk, though we might consider that risks about what is data and risks about accepting hypotheses regarding that data are different kinds of risks, as in Biddle (2016) and Biddle and Kukla (2017).

because a belief that single, anecdotal SADRs do not contribute much to the grand scheme of pharmacovigilance. Say a clinician gives a patient a new medication and an SADR is shortly thereafter observed. The "indifferent" clinician acknowledges that this is an SADR but believes that reporting it would be a waste of time since it is just "this one" SADR, "this one" time. Even though health researchers acknowledge the necessity of anecdotes in building medical knowledge (Enkin and Jadad 1998) and the ability of anecdotes to prove cause–effect relations (Aronson and Hauben 2006), indifference maintains the unimportance of anecdote. This weighing of evidence is a normative activity. We can think about indifference as a kind of aversion to anecdotal evidence in general. *Not* committing this sin would be to report the SADR, anecdote though it may be. Inman believed that physicians played a role as clinical researchers who should be contributing to the advancement of medical knowledge (Lopez-Gonzalez, Herdeiro, and Figuerias 2009). Clinicians may feel that research is distinct from practice; however, the distinction between research and practice in medicine has been acknowledged as epistemically problematic (Bluhm and Borgerson 2018), and the case of indifference is further proof. Notice the relationship between indifference and insecurity: one might be a "secure" clinician and determine something as an SADR but remain indifferent and fail to report it as such.

Finally, let us consider diffidence. Diffidence is the sin in not wanting to appear "foolish" or "ridiculous" (García-Abeijon et al. 2023) in reporting a "merely suspected" SADR, or the belief that reporting should be done only when certain about the causal relationship between the drug and the adverse event (Palleria et al. 2018). Say a clinician gives a patient a drug and they observe an adverse event but hesitate to report it as an SADR because of unknown confounders. Thus, the SADR is not reported as such. Researchers have pointed out that there is a similarity between diffidence and insecurity insofar as they are both kinds of aversions to positing cause–effect relationships in single, uncontrolled clinical observations. Is diffidence reducible to insecurity? Pharmacovigilance researchers still treat them as different, even given the acknowledged relationship (García-Abeijon et al. 2023). I do think they are different enough to justify different treatment as well. A "diffident" clinician might see an SADR as such; that is, be "secure," but still not report. Assume, too, that this diffident clinician is not "indifferent" and recognizes that single case reports might benefit medical knowledge. However, the report may still not occur because of the clinician's not wanting to appear "foolish" or "ridiculous." This shows that diffidence is not identical to insecurity or indifference. There is something else going on here, something about how one sees oneself in relation to other practitioners, which perhaps additionally says something about some professional biases. In the preceding section I argue this is precisely the case and that the roots of diffidence, along with insecurity and indifference, are at least codified in EBM's hierarchical view of evidence.

Before moving on, some summary is warranted. Insecurity, indifference, and diffidence arise as particular value judgments—aversions—in ambiguous cases where there is some kind of epistemic risk. I believe this adds to and augments our understanding of these sins that contribute to underreporting. Notice that with the problem of underreporting in mind, we see why these sins are "bad" instances of values, as they hinder the epistemic aims of pharmacovigilance, such as measuring drug harms. Thinking about these sins and under-reporting in this framework allows us to pinpoint where these sins arise. Aims to mitigate underreporting must aim at changing these aversions. *How* this is done depends on *why*

these specific sins arise, and understanding this is essential for interventions aimed at exorcising the sins.

5. Roots of the Aversions

I contend that the underlying values that constitute the three sins considered here are intimately related. Moreover, I posit that their roots are largely commitments held because of socio-institutional factors. In what follows I show how the aversion to determining an ambiguous event as an SADR (insecurity), the aversion to the significance of single anecdotal cases of SADRs (indifference), and the aversion to speculating cause–effect relationships (diffidence) are at least partially perpetuated because of normative commitments about evidence in EBM; specifically, EBM's entrenched disvalue of anecdotal, noncontrolled evidence.

Traditionally, EBM rests on a hierarchical view of evidence and evidence-generating methods. Hierarchies or "gradings" differ but meta-analyses and randomized controlled trials (RCTs) usually are toward the top; that is, they are considered "good" evidence. Beneath RCTs one usually finds observational, cohort, and case-control trials/studies. Inferences based on mechanisms, expertise, and anecdote are at the bottom of these normative rankings (if they are mentioned at all). Criticisms of this core component of EBM are numerous (for example, Upshur, Kerkhof, and Goel 2001; Bluhm 2005; Cartwright 2007; Worral 2008; Goldenberg 2009; Stegenga 2011; Blunt 2015; Anjum, Copeland, and Rocca 2020; Mercuri, Baigrie, and Gafni 2021).[8] I do not take it as coincidence that this normative ranking of evidence is a core component of EBM while these three sins centered around disvaluing anecdote persist. It is true that Inman posited the sins nearly a decade and a half before EBM's entrenchment in the 1990s. And it would not be right to say EBM causes the sins—that would be anachronistic. It is *not* anachronistic to say that EBM's norms perpetuate or continue the values that underlie the sins. Moreover, philosophers and researchers have already acknowledged that EBM's hierarchical norms about evidence are detrimental to discovering drug harms (Osimani 2014; Stegenga 2016). My point is not radically different than this; rather, it is simply connecting similar concerns to Inman's sins via epistemic risk.

One might object, maintaining that maybe it is true that thinking about epistemic risks can pinpoint specific value judgments or aversions that underlie the sins but this is too far a leap to place blame on EBM. However, looking at EBM guidelines such as the *User's Guides to the Medical Literature,* one notices that "control groups" are stressed even when determining cause–effect relations of SADRs (Guyatt et al. 2015). In the case of pharmacovigilance, we do not need assurance—that is, skepticism of speculation—because the game is to report SADRs, not "proven" adverse drug reactions. That one might not see an ambiguous, isolated event as an SADR is related or coheres to this commitment. In other words, the values that constitute insecurity, indifference, and diffidence as aversions arising in epistemically risky circumstances are at least codified by contemporary EBM. The "foolishness" the diffident clinician feels likely comes from a bias about "good" evidence learned from EBM education. An even more EBM-sympathetic position might be just to say

[8] This is not to say there is *no* justification for "evidence hierarchies" being the way they are—for example, Howick's (2011) qualified defense of hierarchies provides historical and contemporary cases of how *not* operating with EBM's hierarchy in mind has led to not-insignificant medical harms.

that the aims of EBM and the aims of pharmacovigilance are different insofar as the former is about determining drug effectiveness and the latter about determining drug safety. However, I suspect this move to insulate EBM from this criticism removes things from what EBM thinks are within its prerogative—for example, phase IV trials that jointly test hypotheses about effectiveness and explore for unknown side effects (Due 2022). This is not to say something like a Mertonian *organized skepticism* (Merton 1938) is inappropriate in science and medicine, just that as a norm or set of values that underlies *these* sins in *this* context, some address is needed.

Targeting the three sins of note here with the aim of mitigating underreporting entails changing clinician values held with regard to epistemically risky circumstances. By mitigating the aversion to positing an ambiguous adverse event as an SADR, we mitigate insecurity. By mitigating the aversion to positing anecdotal SADR evidence as worthwhile, we mitigate indifference. By mitigating the aversion to speculating cause–effect relations, we mitigate diffidence. By augmenting our understanding of these sins as things that arise because of value judgments in epistemically risky cases, we are provided with a deeper and more detailed set of targets for solutions. And, by putting these sins in an epistemological framework, a bridge is built connecting pharmacovigilance and the epistemologically minded. More perspectives and work on a problem such as underreporting is, I believe, a desirable goal in and of itself. Before closing, let me further apply this framework to one of the mantras of pharmacovigilance considering underreporting: "When in doubt, report."

6. Adding Nuance to "When in Doubt, Report"

The above discussion demonstrates that the considered sins are particular kinds of aversions clinicians have in light of epistemic risk. In other words, here I have demonstrated how the epistemic risk framework augments what are taken to be some causes of under-reporting. It can also augment or add nuance to what is taken to be a solution to under-reporting, which is embodied by a common mantra one finds in pharmacovigilance: "When in doubt, report" (for example, Naina-Mohamed 2014; Viljoen and Muntingh 2022). One even finds this sentiment in official regulatory guidelines. Recent guidelines from the South African Health Products Regulatory Authority claim that in the post-market context, in cases of uncertainty, one ought to report anyhow (SAHPRA 2022, 13). The epistemic risks framework adds nuance to this sentiment in two ways: articulating what kind of "doubt" is relevant and addressing *over*reporting.

Firstly, what is meant by "doubt" in the context of "when in doubt, report"? It seems to be a doubt regarding cause–effect relations, specifically between an intervention and some adverse event or patient experience. The idea is that because of pharmacovigilance's aim of determining drug safety, one ought to err on the side of positing a false positive (that something is a worthwhile-to-report SADR even if it is not). The problem of underreporting is a problem about a lack of data and "when in doubt, report" aims to bring that 95 percent unreported rate down. Clinicians who claim they have no "doubts" that some adverse patient experience is not an SADR of a novel drug may be ignorant or complacent about the problem of underreporting or, if this is willful, it belies value judgments. One ought to respond to doubt by assuming reporting is useful rather than assuming it is not, since both claims are empirically provable only after pharmacovigilance analyses that require these reports in the first place. Additionally, this shows that "when in doubt, report" is not about

doubt unrelated to that cause–effect relation between the intervention and some adverse patient experience. This may seem trivial to highlight but it is a point that now stands with more justification given the risks framework. Considerations of doubt may change outside the context of underreporting; different problems require different solutions and different applications of frameworks.

Second, the epistemic risks framework theoretically precludes the possibility of *over*-reporting, where underreporting would be over-mitigated to the point where pharmacovigilance researchers are overwhelmed with reports. An imaginary case of overreporting may be a problem depending on storage and computation capacities, or it may be a problem insofar as it de-prioritizes face-to-face care in clinical settings. Either way, this imaginable scenario is theoretically precluded, as we would recognize that the cause of this problem would likely be because of a value or values. Since the epistemic risk framework tells us that whenever values infringe on epistemic aims, such as those we would imagine being infringed upon in the case of overreporting, they are values to be replaced. We ought to be reflexive in whatever values underlie our pharmacovigilance practices.

7. Conclusion

Insecurity, indifference, and diffidence are aversions; that is, consequences of values, to positing phenomena as worthwhile-to-report SADRs in epistemically risky circumstances. Mitigating these sins requires addressing normative commitments around evidence that I have argued are perpetuated by tenets of EBM. Admittedly, these three sins are not as prevalent or impactful as ignorance and lethargy. However, where something like ignorance can be mitigated by simple educational interventions and lethargy by incentivization, the three sins discussed here require something more detailed. We can inform clinicians that reporting SADRs is important but, unless that intervention also addresses the causes of insecurity, indifference, and diffidence, the intervention will fall short of tackling underreporting in any comprehensive way.

However, dealing with underreporting will require more than just addressing the sins; systematic and institutional factors, such as patient volume, face-to-face time, technology, and so on, play a role in underreporting (Hohl et al. 2018). Modern medicine is just not designed to maximize pharmacovigilance's aims. Also worth mentioning as a limitation to this analysis is that the sins fall squarely on the shoulders of healthcare professionals and ignore a role for patients, who may be taking up a more active role in pharmacovigilance (Due forthcoming). In short, more detailed causes of the sins of insecurity, indifference, and diffidence can be pinpointed when we consider them in the epistemic risk framework. At the very least, this augments our understanding of underreporting, which is itself valuable given its impact and scope. With a problem as complex and systemic as underreporting, something as simple as articulation from a variety of perspectives may be useful to those pursuing concrete solutions.

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