

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 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 posit that 90% to 95% of SADRs go unreported to regulatory bodies and databases (Hazell & Shakir 2006; Lopez-Gonzalez, Herdeiro, & Figuerias 2009; Hohl, Small, & Peddie et al. 2018). Since these reports form the foundations of pharmacovigilance research, the problem of underreporting is a major hinderance 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 pharmacoepidemiologist and pharmacovigilance pioneer W.H.W. Inman. Inman’s ‘deadly sins’ are attitudes or influences clinicians have 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* that a single SADR matters in the ‘grand scheme’ of medical knowledge, *insecurity* in positing some adverse event as a SADR, and *diffidence* at ‘mere speculation’ of cause-effect relations in clinical observations (Inman 1976; Inman & Weber 1986; Lopez-Gonzalez, Herdeiro, & Figuerias 2009; Palleria, Leporini, & Chimirri 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, & Figuerias 2009; García-Abeijon, Coast, & Taracido et al. 2023). Therefore, interventions aimed 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. Secondly, 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 disvalue of anecdote. This is evident when looking at EBM guidelines like the ‘User’s Guide to the Medical Literature’ which states that control variables are needed to posit some phenomenon as a SADR (Guyatt, Rennie, Meade & Cook 2015). Philosophers of medicine have already highlighted issues with drug safety monitoring and EBM (e.g., Osimani 2014; Stegenga 2016). I merely mean 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 articulates them over a decade before EBM’s entrenchment in the 1990s. Nor am I positing that mitigating the sins alone solves underreporting. The sins are just one – albeit a significant one – component of underreporting, as institutional features that individual clinicians have no control over also contribute to underreporting (Hohl, Small, & Peddie et al. 2018). Thirdly, 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 towards mitigating underreporting. The analysis here 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 towards solutions.

In arguing for the above, 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 then 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 Underreporting, & 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 around the safety and misbranding of medicines containing heroin, alcohol, and cocaine. The 1938 Federal Food, Drug and Cosmetic Act endowed the FDA with power to reject market access to medicines, spurred on by the sulfanilamide disaster where 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 pre-market requirements of new drugs, was spurred on by the thalidomide disaster where 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 (Kim & Scialli 2011).

Over six decades later, the need for pharmacovigilance remains paramount, especially considering recent disasters and controversies like rofecoxib (Wadman 2005), oxycodone (Van Zee 2009), and aducanumab (Brockmann, Nixon, Love, & Yunusa 2023), among others. Well-over 100,000 people die each year from adverse drug reactions, many thought to be preventable (Light, Lexchin, & Darrow 2013). Adverse drug reactions are estimated to be in the top 5 leading causes of death in hospital settings (García-Abeijon, Coast, & Taracido 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, & Aronson 2016). To detect a 1 in 10,000 occurring adverse reaction or side effect² of

¹ Though, 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, i.e., 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.

some novel drug, a 95% power detection method requires 30,000 patients to have taken that novel drug (Mohamed 2014). Most clinical trials just simply are not that big. And, this problem of detection is compounded when we add ubiquitous considerations of co-morbidity and polypharmacy.

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 but had a teratogenic adverse effect of cancer (Herbst, Ulfelder, & Poskanzer 1971). The FDA continues to collect SADR reports through online resources like MedWatch and the FDA Adverse Event Reporting System (FAERS). In the US, patients can report their SADRs to the FDA as well, something that the average patient likely does not know.³ Similar databases exist in other countries and through the World Health Organization (WHO), and non-government reporting services like RxISK.org also exist. When enough SADRs are collected about some drug and some effect is determined as significant by regulators, investigations begin that may not have otherwise been done. For that reason, spontaneous reporting is often touted as the ‘cornerstone’ of pharmacovigilance (Moore 2014). Spontaneous reporting has successfully caused the removal of dangerous drugs from the market, including fenfluramine, terfenadine, mibefradil, bromfenac, astemizole, grepafloxacin hydrochloride, cerivastatin sodium, and has led to increased regulation on drugs like isotretinoin, clozapine, and fentanyl, among others (Wysowski & Swartz 2005).

However, it is estimated that up to 95% of SADRs go unreported to regulatory bodies and databases (Hazell & 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 side effect discovery process. Underreporting is caused at an institutional level (Hohl, Small, & Peddie 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

³ Patients both average and not-so in the US may not know reporting SADRs is available via <https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting>.

⁴ The Hazell & Shakir (2006) paper has been cited over 2000 times, at least as of March 2024.

clinician and health care provider inaction as well, or at least is so posited by Inman's 'deadly sins.' As above, Inman's secular sins and their recent amendments are attitudes⁵ that prevent reporting SADR: *complacency* is the sin of believing only safe drugs are allowed on the market, so whatever adverse event a patient is experiencing is not a 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 at having harmed a patient and assumedly 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 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 a SADR; *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 & Weber 1986; Lopez-Gonzalez, Herdeiro, & Figuerias 2009; Palleria, Leporini, & Chimirri et al. 2013). Mitigating underreporting means mitigating the sins; doing so is a primary goal for pharmacovigilance.

A 2009 review of empirical data on underreporting by Lopez-Gonzalez et al. found that ignorance was responsible or played some role in 95% of cases of failed reporting, followed by lethargy at 72% of examined cases. A 2023 update of this review done by members of the same team found that ignorance and lethargy remain at the forefront of the sins responsible for underreporting (García-Abeijon, Coast, & Taracido et al. 2023). However, the 2009 review also found diffidence, indifference, and insecurity to play a role in at least 67% of examined cases. The 2023 review found that complacency in 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 respectively 27.7%, 33.8%, and 44.6%. Even if something like indifference is only responsible for 1 of every 4 or so 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 health care 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

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).

beyond addressing ignorance and lethargy, including things like insecurity, indifference, and diffidence. Articulating and augmenting our understanding of these in epistemological terms now follows.

3. Epistemic Risk and Values

Values play a major role in scientific practice. Whether or not or to what degree they should is an ongoing conversation in the philosophy of science (e.g., Betz 2013; Holman & Wilholt 2022) outside the scope of this paper. Either way, 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' (2000) account of how values play a role in data characterization and standards of evidence.⁶ Douglas discusses a trial determining if a particular toxin caused tumors in animal subjects. Determining whether the suspected tumors were caused by the toxin was ambiguous, i.e., there was a risk of inferring a false-positive (the toxic 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 like '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, i.e., 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.

This inductive risk of hypothesis acceptance is a subset of a more general type of risk: *epistemic* risk, i.e., the risk of being wrong. Justin Biddle and Quill Kukla (2017) highlight that within epistemic risk,

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

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, p. 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 both differed on whether or not the image constituted an abnormality, it would likely be due to different values considering phronetic risk. For example, one may be concerned with complications from over-diagnosis, the other from under-diagnosis (Biddle 2016). In other words, when there are epistemic risks, e.g., 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 or not the value in question is impacting the epistemic progress or aims. Some value like ‘simplicity’ might better achieve some epistemic goal of communication or understanding even if it idealizes content. Values like ‘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 re-balance those values. In short, when there are uncertainties and risks, non-epistemic values arise. These values guide actions and decisions in ambiguous circumstances, whether it is 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 over-diagnosis of some condition going on, bad values are likely a key culprit and must be a target of change. The following shows how this is mirrored in the sins of indifference, insecurity, and diffidence.

4. Insecurity, Indifference, & Diffidence as Aversions

Let’s start with insecurity. Insecurity was not originally proposed by Inman but has since found its way into the list of sins (Lopez-Gonzalez, Herdeiro, & Figuerias 2009). Insecurity is the sin of

⁷ This is something Douglas (2000) also considers 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 is done by Biddle (2016) and Biddle & Kukla (2017).

encountering an ambiguous adverse patient experience and based on that ambiguity failing to ‘see’ it as a SADR. The ‘insecure’ clinician sees the ambiguous event and concludes that it is not a 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 judgement – due to epistemic risk. *Not* committing the sin of insecurity would be to ‘see’ the ambiguous event as a SADR.

The sin of indifference describes cases unlike insecurity insofar as a clinician acknowledges some phenomenon is a SADR. However, there is still a failure to report 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 a SADR is shortly thereafter observed. The ‘indifferent’ clinician acknowledges that this is a SADR, but believes that reporting the SADR would be a waste of time since it is just ‘this one’ SADR ‘this one’ time. Even though health researchers acknowledge the necessity of anecdote in building medical knowledge (Enkin & Jadad 1998) and anecdotes’ ability to prove cause-effect relations (Aronson & 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, & 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 & 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 a SADR but remain indifferent and fail to report.

Finally, let’s consider diffidence. Diffidence is the sin in not wanting to appear ‘foolish’ or ‘ridiculous’ (García-Abeijon, Coast, & Taracido 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, Leporini, & Chimirri et al. 2018). Say a clinician gives a patient a drug and they observe an adverse event, but they hesitate report it as a 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, Coast, & Taracido et al. 2023). I do think they are different enough to justify different treatment as well. A ‘diffident’ clinician might ‘see’ a SADR as such, i.e., 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 not wanting to appear ‘foolish’ or ‘ridiculous.’ This belies 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 belies some professional biases. In the proceeding 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 judgements – 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 like measuring drug harms. Thinking about these sins and underreporting 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 a 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, non-controlled evidence.

Traditionally, EBM rests on a hierarchical view of evidence and evidence-generating methods. Hierarchies or ‘gradings’ differ, but meta-analyses and randomized control trials (RCTs) usually are towards the top, i.e., 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 mentioned at all). Criticisms of this core component of EBM are profuse⁸ (e.g., Upshur, Kerkhof, & Goel 2001; Bluhm 2005; Cartwright 2007; Worrall 2008; Goldenberg 2009; Stegenga 2011; Blunt 2005; Anjum, Copeland, & Rocca 2020; Mercuri, Baigrie, & Gafni 2021). 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 devaluing anecdote persist. It is true that Inman posited the sins nearly a decade and a half before EBM’s entrenchment in the 1990s. 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 (Osmani 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 that it is too far a leap to place blame on EBM. However, looking at EBM guidelines like the ‘User’s Guide to the Medical Literature,’ one notices that ‘control groups’ are stressed even when determining cause-effect relations of SADR (Guyatt, Rennie, Meade, & Cook 2015). In the case of pharmacovigilance we do not need assurance – i.e., skepticism of speculation – the game is to report SADR, not ‘proven’ ADRs. That one might not ‘see’ an ambiguous, isolated event as a SADR is related 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 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

⁸ That is not to say there is *no* justification for ‘evidence hierarchies’ being the way they are, e.g., 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.

things from what EBM thinks are within its prerogative, e.g., phase IV trials which 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.

Summing up, targeting the three sins of note here with the aim of mitigating underreporting entails changing clinician values held considering epistemically risky circumstances. By mitigating the aversion to positing an ambiguous adverse event as a 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 hands on a problem like 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 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 underreporting. It can also augment or add nuance to what is taken to be a solution to underreporting, which is embodied by a common mantra one finds in pharmacovigilance: ‘when in doubt, report’ (e.g., Mohamed 2014; Viljoen & 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, p. 13). The epistemic risks framework adds nuance to this sentiment in two ways: articulating what kind of ‘doubt’ is relevant and addressing *overreporting*.

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% unreported rate down. Clinicians that may claim they have no ‘doubts’ that some adverse patient experience is not a SADR of a novel drug may be ignorant or complacent of the problem of underreporting, and if this is willful then it belies value judgments. One ought to respond to doubt by assuming reporting is useful rather than assuming that 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.

Secondly, the epistemic risks framework theoretically precludes the possibility of *overreporting*, 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 like 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, i.e., consequences of values, to positing phenomena as worthwhile-to-report SADR in epistemically risky circumstances. Mitigating these sins requires addressing normative commitments around evidence that I 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 SADR is important, but unless that intervention also addresses the

causes of insecurity, indifference, and diffidence the intervention will fall short of more comprehensively tackling underreporting.

However, tackling underreporting will require more than just addressing the sins; systematic and institutional factors like patient volume, face-to-face time, technology, etc. play a role in underreporting (Hohl, Small, & Peddie 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 health care 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.⁹

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