Is There a 'Best' Way for Patients to Participate in Pharmacovigilance?

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Abstract
The underreporting of suspected adverse drug reactions hinders pharmacovigilance. Solutions to underreporting are oftentimes directed at clinicians and health care professionals. However, given the recent rise of public inclusion in medical science, solutions may soon begin more actively involving patients. I aim to offer an evaluative framework for future possible proposals that would engage patients with the aim of mitigating underreporting. The framework may also have value in evaluating current reporting practices. The offered framework is composed of three criteria that are bioethical, social-epistemic, and pragmatic: (i) patients should not be exposed to undue harms, e.g., nocebo effects; (ii) data should be collected, analyzed, and communicated prioritizing pharmacovigilance's aims, i.e., free from industry bias; and (iii) proposals should account for existing and foreseeable pragmatic constraints like clinician 'buy in' and existing reporting infrastructure. Proposals to engage patients in pharmacovigilance that fulfil or address these criteria are preferable to those that do not.

Keywords: pharmacovigilance; underreporting; participatory research; citizen science; nocebo effects.

1. Introduction

Post-market pharmaceutical surveillance or 'pharmacovigilance' aims to monitor drug safety. A cornerstone of pharmacovigilance is the 'spontaneous reporting' of suspected adverse drug reactions (SADRs) to regulatory databases. From these reports, signals can be detected that prompt study into drugs' side effects that may have not been known about in the pre-market trial process. However, it is estimated that over 90% of SADRs go unreported (Hazell & Shakir 2006; Lopez-Gonzalez et al. 2009). This problem – *the problem of underreporting* – significantly hinders pharmacovigilance. The problem of underreporting is often thought to be caused by the inaction of clinicians. Pharmacovigilance pioneer W.H.W. Inman posited that underreporting was the consequence of secular 'deadly sins' clinicians commit like being complacent in the safety of market-approved drugs, lethargy in reporting, and ignorance in knowing how to report, among others (Inman 1976; Inman & Weber 1986). Others have highlighted that underreporting persists because of institutional factors like patient volume, time constraints on clinicians, and a lack of utilization of available technologies like electronic health records (EHRs) (Hohl et al. 2018). Various solutions have been suggested for underreporting ranging from establishing professionalization programs (Kugener et al. 2021), enforcing mandatory reporting (Lemmens & Gibson 2014), and collecting or linking EHRs

(Sturkenboom 2021). However, these are mostly directed at health care professionals. And, health care professionals are not the only ones who can report SADRs to regulatory databases – *patients* can too.

Patients in the US can report SADRs directly to the US Food and Drug Administration (FDA).[1] Most patients, however, do not know this. Moreover, patients do not often see themselves as responsible for reporting their SADRs (Paola & Claudio 2020). Patient reporting *is* on the rise in countries that maintain such databases, but underreporting persists (Matos 2019). So, it may be the case that solutions to underreporting that focus on clinicians are too narrow. It may be the case that patients need to be engaged to mitigate underreporting, and this becomes more of a possibility as time goes on with rising interest in patient engagement and participation in medicine. Encouraging patients to mitigate underreporting would take the form of making patients attentive to SADRs with the aims of reporting. However, there are foreseeable harms, social-epistemic issues, and pragmatic issues when we consider how this should be done – if at all.

My aim here is to offer a guiding framework to evaluate future possible proposals that would aim to mitigate underreporting via patient participation. This framework is useful given the steep rise of patient engaged research and its funding in the health sciences (Snape et al. 2014; Harrison et al. 2019). And while the ethics of patient engaged research in medicine is ongoing (e.g., Wiggins & Wilbanks 2019), this remains underexplored in the pharmacovigilance context (Paola & Claudio 2020). One might immediately object, claiming that we just ought not have patients participate in pharmacovigilance with the aim of mitigating underreporting. I grant that this is a possibility. However, *if* patient participation was used to mitigate reporting, then it is useful to know which ways are better and which ways are worse. In other words, my aim here is to answer the question and begin thinking about if we did engage patients to mitigate underreporting, what is the *best* way in which it could be done?

Answering this question requires (1) an understanding of what the mode or type of patient participation would be necessary with underreporting in mind and (2) determining how we ought to prevent or mitigate the foreseeable bioethical, social-epistemic, and pragmatic issues. In what follows, I address (1) by surveying recent work on participation in science. I argue that for the problem of

[1] https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting. Accessed Jun 2022. Non-government pharmacovigilance databases also exist like RxISK.org.

underreporting – a problem constituted by a lack of data – the most appropriate mode of participation is what scholars have identified as *contributory* participation. I address (2) by offering a framework composed of criteria that mirror the bioethical, social-epistemic, and pragmatic foreseeable issues of such a project. The criteria are (i) patients should not incur undue harms, e.g., nocebo effects from being encouraged to 'hunt' for SADRs or violations of data autonomy/privacy, (ii) SADR reports ought to be collected, analyzed, and communicated prioritizing pharmacovigilance's aims of drug safety, i.e., free of conflicts of interest from industry biases, and (iii) proposals must account for pragmatic constraints, e.g., the 'buy in' of researchers, clinicians, and the public, as well as constraints regarding existing reporting infrastructure. Proposals that fulfil or address these criteria will be preferable to those that do not.

In what follows, I first briefly discuss the problem of underreporting in section 2. Section 3 surveys recent work theorizing and taxonomizing participation in science and medicine to determine the proper role of patients in the context of mitigating underreporting. Section 4 then considers some thought experiments instantiating patient involvement to mitigate underreporting in order to highlight the foreseeable bioethical, social-epistemic, and pragmatic issues. Section 5 develops the three criteria that compose the evaluative framework in light of these issues. Section 6 then highlights some limitations to this analysis, thereafter concluding in section 7.

2. Underreporting & Pharmacovigilance

Pharmacovigilance is a necessity in modern medicine. There is a gap in our knowledge about the safety of many pharmaceuticals, especially novel ones. This gap is often thought to be due to a combination of *laissez-faire* regulation (Lexchin 2016) and the shortcomings of pre-market drug trials (Sismondo 2008; Stegenga 2016). We usually do not know all the side effects or adverse reactions[2] of a drug until it has already been on the market for some time (Onakpoya et al. 2016). Reporting SADRs is necessary to determine information about these harms and is the cornerstone of pharmacovigilance. Reporting is the data-gathering process required for confirmatory studies and analyses to determine drug effects, both positive and negative. However, estimates posit that over 90% of SADRs go unreported (Hazell & Shakir 2006), constituting the core issue of underreporting: a lack of incorporating available data.

[2] Strictly speaking, 'side effects' and 'adverse reactions' are different things, though they can overlap when some phenomena is unintended, adverse, and due to the causal powers of a drug (Due 2023).

Without better SADR reporting, pharmacovigilance's power to monitor the safety of drugs is hindered, contributing to preventable patient harms.

Spontaneous reporting has a track record of pulling unsafe drugs from the market and facilitating label changes and 'black box'-ing[3] useful but dangerous drugs (Wysowski & Swartz 2005). It is estimated that with proper reporting, Vioxx (rofecoxib) could have been pulled from the market in as little as three months post-approval, which could have saved thousands of lives (Sturkenboom 2021). Given that well-over 100,000 people die each year from adverse reactions, and that these are a leading cause of death in hospital settings (Light et al. 2013), we have concrete, immediate reasons to see that underreporting is a problem worth solving. That *patients* may be encouraged to play more of a role in pharmacovigilance via either their own accord or through the intentional action of researchers may be on the horizon as a live option. And, precedents for this exist to some degree. The Netherlands developed a 'Pharmacovigilance Centre' in 2003 where now, patient reports outnumber all other sources (Paola & Claudio 2020). In addition, patients already often report their SADRs on social media (Golder et al. 2021). In short, the problem of underreporting in pharmacovigilance is a problem about a lack of collecting available SADR data, and it is an important problem to solve as it contributes to preventable costs, harms, and deaths.

3. Varieties of Public-Engaged Research

Public involvement in the sciences has roots going back over a century, though its recent rise coincides with social movements and lay scrutiny (Evans & Potochnik 2023; Kimura & Kinchy 2016). Many health journals and funding bodies now actively encourage public inclusion (Harrison et al. 2019). Bodies like the Canadian Institute of Health Research (CIHR) have initiated programs on citizen engagement described as the 'meaningful involvement of individual citizens in policy or program development.'[4] Various umbrella terms exist for research where the public is engaged and plays some part in the research process, from 'citizen science' (Kimura & Kinchy 2016) to 'participatory research' (Dunlap et al. 2021) to 'community science' (Kovaka 2021) to 'patient/public involvement or engagement' (Frith 2023). Different disciplines and approaches have different historical and

[3] Having a 'black box' warning is the harshest FDA regulation for market-approved drugs, analogous to the 'red list' in the UK's NHS.

[4] More on the CIHR's program can be found at https://cihr-irsc.gc.ca/e/41592.html. Accessed June 2022.

conceptual relationships to this kind of research, so clean-cut distinctions across disciplinary lines are tricky (Peters et al. 2021). In what follows I will use 'participatory research' to refer to contexts where patients or the public are involved in research, though nothing of note bears on the terminology. One could substitute 'patient community science' or 'patient citizen science' if so inclined. To first determine what the 'best' way for patients to participate in pharmacovigilance with the aim of mitigating underreporting might be, we first need to understand what kinds or types of participatory research are on offer from which to take precedent.

One way to delineate different kinds of participatory research is by looking at the role or function of public participants. A taxonomy based on this is proposed by Shirk et al. (2012), dividing participatory research into five categories. The first is *contractual* participation where members of the public ask scientists to carry out some specific task on the public's behalf. An example of this might be a case where a group of patients with an unknown novel illness seek out a team of researchers to diagnose or treat this illness. The research is done at the behest of the patients, but the methods and analysis are done solely by professionals. The second type of participation is *contributory* participation where members of the public donate or volunteer data to a project initiated and carried-out by professional researchers. An example of this might be cases of voluntary responses to patient-reported outcome measures (PROMs) after surgery. The third kind of participation is *collaborative* participation where members of the public help define and revise a project ran by scientists and may help in the actual analysis and dissemination of results. An example of this might be community-based participatory research (CBPR) in environmental and health justice research,[5] where members of the public actively work alongside professional researchers who often begin and facilitate such projects. The fourth kind of participation is *co-created* participation where a project is jointly initiated by the public and professionals and the public is involved in all or most of the research process. An example of this might be the 1997 study on thalidomide for HIV-related 'wasting' ran jointly by health researchers and activists in the San Francisco Bay Area (Sharpe et al. 1997). Finally, there is also *collegial* participation where projects are run solely by members of the public with various degrees of recognition from professional researchers. Instances of this might be 'n-of-1' self-tracked 'trials' that patients run that generate information that may or may not be used by their clinicians in treatment plans.

[5] CBPR tends to be contrasted with 'helicopter' research where researchers enter a community, make measurements, leave, publish results, and nothing of note occurs for or to that community.

The functions or roles of the public are not the only ways to delineate or taxonomize participatory research. Kimura & Kinchy (2016) highlight that different instances of participatory research yield or support different virtues including: increasing data, expanding literacy, building capital, community leadership, leveling inequality, challenging authority, supporting social justice, driving policy, and catching polluters in the ecological context. For example, CBPR is traditionally aimed at leveling inequalities, building community capacities, or enacting regulatory change (Peters et al. 2021). By necessity CBPR might create new data, but the creation of new data is not the main reason why CBPR occurs. On the other hand, volunteers monitoring flora and fauna in their yards increases data for scientists but does not necessarily instantiate the virtues of CBPR. In short, from Shirk et al. (2012) and Kimura & Kinchy (2016) we have two different ways to analyze participatory research insofar as modes of engagement and virtues instantiated.

Dunlap et al. (2021) and Evans & Potochnik (2023) further highlight that these values can be delineated along epistemic, practical, communal, societal, and political lines. Moreover, these virtues are perspectival. For scientists, the goals of bringing the public into a project might be epistemic, i.e., the creation or access to new data. But for members of the public, say in the flora and fauna case, reasons for engaging might be to build literacy, or because of personal enjoyment which Dunlap et al. (2021) identify as a 'practical' goal. Moreover, from Evans & Potochnik (2023) we get a list of goal-relevant questions to use in analyzing specific participatory practices, e.g., what are the primary goals for researchers, what are the primary goals for participants, why are scientists including the public, why is the public working with scientists, what methods are in place to achieve these goals, how are power differentials addressed, how do the goals shape the research agenda, whose expertise is relevant to achieve these goals, what are the ultimate virtues of the project, and how should scientists be involved with participation?

From the discussion of Shirk et al. (2012), Kimura & Kinchy (2016), Dunlap et al. (2021), and Evans & Potochnik (2023) we get a detailed taxonomy or framework with which to discuss and analyze participatory projects regarding functions of the public and virtues or goals. With this in mind, let us return to the question of this paper. Here we are asking if there is a 'best' way for the public to be involved with pharmacovigilance, specifically with the aim of mitigating underreporting. Answering that question requires (1) looking at the proper mode of participation and (2) how to judge better from worse proposals. We are now in a position to answer question (1).

Given that the problem of underreporting is primarily about a lack of data, i.e., that nearly 90% of SADRs go unreported to regulatory databases, this tells us that the primary goal of a participatory project aimed at underreporting is epistemic, i.e., data gathering. This is not to say that motivations to report SADRs are always merely epistemic, just that with the problem of underreporting being the motivation for reporting, this motivation is an epistemic one. Or at least, these would be the goals of researchers. Patient goals might also be epistemic insofar as the data gathered is essential for informing patient decisions, but practical goals might also play a role. What about the methods in place to achieve these goals, how power differentials are addressed, and how goals shape research agendas? Answering these, I posit, is easier when we see what the role of patients must minimally be in these contexts, i.e., determining which kind of participation offered by Shirk et al. (2012) is appropriate.

I argue that the most appropriate kind of participation given the problem of underreporting is *contributory* participation. The problem of underreporting is an epistemic problem. Increasing data is an epistemic goal. Patients being involved in this process would likely not be running trials on their own, ruling out collegial participation. Regulatory databases are already in place, ruling out co-created projects. Patients are not performing statistical analyses or running phase 'IV' trials, ruling out collaborative participation. The problem of underreporting is not about investigating any particular set of concerning SADRs that patients might worry about, but about SADRs in general, ruling out contractual participation. In other words, the most appropriate form of participation in the imagined case where we actively involve patients in pharmacovigilance with the aim of mitigating underreporting would be as contributors of data, specifically, SADRs. The role of patients reporting SADRs is more like the PROMs case or the case of reporting flora and fauna in yards, and less like the cases of CBPR or Sharpe et al. (1997). With contributory participation, the methods in place to achieve the goal of mitigating underreporting must facilitate contributions from patients, the research agenda must have this goal in mind, and power differentials must be addressed similarly to other biomedical interventions with autonomy and informed consent in mind.[6]

In short, because the problem of underreporting is foremost an epistemic problem about a lack of data, the way we would engage patients in participation must have epistemic aims in mind, e.g., gathering and reporting SADR data. A contributory mode of engagement is the minimally required

[6] I will leave the specific details of shaping the goals vague, as these will change and be more specified depending on the concrete contexts and idiosyncrasies of possible proposed projects.

kind of participation for this. Thus, we have an answer to question (1) regarding the proper mode of participation for patients mitigating underreporting. That is not to say the other modes of participation are categorically inappropriate; they may be permissible if they meet the criteria that follow in the proceeding sections. However, given those criteria, specifically concerns about pragmatic constraints, contributory participation as the minimally required kind of participation to mitigate underreporting is likely the 'best' form for our context here. With that in mind, we are now in a position to discuss these criteria that make up the evaluative framework, i.e., question (2) about how we could evaluate better from worse instances of calls for contributory participation that aim to mitigate underreporting. To do this, let us first imagine a few different implementations of such a system and see where foreseeable issues arise. From addressing and considering those issues, the three criteria that compose the evaluative framework become apparent.

4. Imagined Implementations

In what follows I present three possible abstract implementations of contributory patient participation with the aims of mitigating underreporting. The purpose of these imaginary implementations is to see where foreseeable issues arise. In considering where these issues arise, we can formulate criteria that will compose the evaluative framework. As I will show, the foreseeable issues that arise will be broadly bioethical, social-epistemic, and pragmatic. And thus, the criteria that compose the evaluative framework – a framework that would allow us to judge better from worse suggestions about patients mitigating underreporting – will mirror these three types of concerns.

One possible implementation of contributory participatory research aimed at mitigating underreporting may be where patients take it upon themselves without prompt from their physicians to report SADRs.[7] Reporting could be done through existing databases, the development of new or existing mobile applications and technologies, or via compiling reports from social media. The proportion of SADRs reported via social media is similar to proportions reported in clinics (Golder et al. 2021). This approach could be simple, wide-spread, and accessible to anyone with an internet connection. Patients would be encouraging other patients to look out for SADRs in order to report them to regulatory bodies to bridge the gap in SADR data without doing the formal causal or statistical

[7] On all the imagined approach or implementations, we will assume that regulatory bodies continue to function as they currently do.

analyses themselves. We might think of this as a 'patient-dominant' approach where patients actively report their SADRs, largely removed from clinician interactions and directly to databases.

Another imagined implementation would be one where patients do not initially seek out amongst themselves to report but are spurred on by private industry. This is also not without precedent. The rise of participatory research and the 'participatory turn' has not gone unnoticed by private industry. Corporate funded participatory research or 'public relations citizen science' initiatives are increasingly popular (Blacker et al. 2021). In the pharmaceutical context, we might imagine a case where a private company has a new drug and funds a contributory approach where patients are encouraged to report their SADRs directly to the company. The collection, analyzing, and reporting of these SADRs is done by the private company itself. We might think of this as an 'industry-dominant' approach.

A final imagined case will be sufficient for showing a spectrum of where foreseeable issues can arise in cases of contributory participation aimed at mitigating underreporting. Imagine a case where patients are prescribed drugs, and the patient's SADRs are tracked by the patient *in consultation* with their physician. All SADR reporting would be done by the clinician or by the patient with the clinician together. This might look similar to 'n-of-1' trials where clinical research and treatment blur, and this would be instantiated for every patient taking medications and a part of every physician's practice. We might think of this as the 'patient-physician' approach.

The different approaches laid out here – patient-dominant, industry-led, and patient-physician – are intentionally abstract. Their purpose is to reveal where foreseeable issues can arise in the implementation of contributory participation aimed at mitigating underreporting. Some may be intuitively better and some intuitively worse, but all are obviously imperfect. Highlighting what those imperfections and issues are reveals three kinds of places where things can go wrong. From considering these we arrive at three criteria that future concrete suggestions ought to address should they arise.

5. Issues with Implementations & Developing the Evaluative Framework

In considering the imagined cases in section 4, we can see that there are broadly three kinds of foreseeable issues that can arise in cases of contributory participation aimed at underreporting: bioethical issues/harms, social-epistemic issues, and pragmatic issues/constraints.

Thinking first of the patient-dominant approach, something that we can foresee going wrong is the proliferation of nocebo effects. Nocebo effects are the negative counterpart to the placebo effect, and usually are thought to be due to negative framing, expectations, or conditioning (Friesen 2020). We can imagine that in the patient-dominant approach, individuals would be encouraged to 'hunt' for SADRs by their peers who might be poorly framing risks. Nocebo effects are genuine harms and ought to be prevented. This does not mean barring patients from knowing possible side effects of drugs, just that proper risk communication is necessary insofar as it does not create undue negative expectations or conditioning.[8] In other words, something that we can foresee going wrong in the patient-dominant approach is the proliferation of nocebo effects from poor framing of SADRs, which seems to be a bioethical harm in terms of unneeded and preventable harms occurring to patients. Another thing we can foresee going wrong in the patient-dominant approach is the violation of data privacy or autonomy through things like novel mobile applications. SADRs might belie information that patients do not want spread or leaked to the general public, and a patient-dominant approach that utilizes social media or mobile applications to collect SADR data to mitigate underreporting runs this risk. This also constitutes a kind of bioethical harm insofar as a risk to privacy and autonomy. The nocebo effect as a harm is something that we can also foresee in the industry-led and patient-physician approach.

Not only are nocebo effects harmful, but if a nocebo effect is reported as a SADR this is 'noise' in a SADR database. It is true that a nocebo effect when experienced is a SADR, but the purpose of reporting SADRs is to later determine what the ADRs of a drug are. And, in the case of pharmaceuticals, nocebo effects are not ADRs (Due 2023). Or, we might just say that the aim of SADR reporting is to collect non-nocebo SADRs, meaning we ought to avoid causing nocebo effects in these cases.[9] In other words, nocebo effects also constitute a problem with the epistemology of solving underreporting insofar as they are 'noise' in databases.

Nocebo effects are not the only epistemic problem foreseeable in these cases. What about risk framing that occurs in such a way that SADRs are *ignored?* We could imagine this occurring in the industry-led

[8] Howick (2020) discusses in detail how risks can be presented in ways that more or less cause negative expectations.

[9] My thanks to a reviewer for this offered response.

approach where the industry wants to down-play SADRs. The industry-led approach would also be a legal minefield (Materia et al. 2020). Given the interests of private industry, the risks of SADRs might be framed too lightly, and patients might be encouraged not to report unless they are 'certain' a SADR is an ADR. Industry-led risk framing might influence the assumptions of patients around what are or are not 'worthwhile to report' SADRs. Industry bias could also arise in the patient-dominant approach through things like 'astroturfing' or in the patient-clinician approach via conflicts of interest. All these could lead to patients experiencing a SADR and not reporting, constituting an epistemic and social-epistemic issue that remains central in underreporting.

Other social-epistemic issues with the industry-led example include issues often brought up by philosophers. A private company's accumulated data could be used to discredit outside independent claims about the drug's safety. When a public or non-profit group claims that a new pill is harmful, the private company can reply with its own 'evidence,' citing that it is collecting data in a more 'fair' and 'democratic' way; the act of collecting the data can be highlighted by the company to seem more 'rational' than special interest groups focused explicitly on safety (Blacker et al. 2021). The data could be 'cleaned' or interpreted favorably when it is ambiguous (Hicks 2014). Furthermore, under the guise of 'industry secrets' private companies might not share or make open their accrued data. Private industries are not required to disclose their trial data about drugs already on the market.[10] Moreover, in the communication of reported data, private industry could frame risks in manipulative ways with trusted physician influence through nefarious ghost-writing practices (Fugh-Berman 2010). Possibly harmful drugs might stay on the market longer *even with* increased reporting if transparency[11] is not maintained. These possibilities cause patient harms and run against the social-epistemic goals of pharmacovigilance, i.e., understanding and preventing drug-related harm.

As above, bioethical issues about nocebo effects and data violation might be applicable in the patient-physician approach, as well as social-epistemic issues like industry bias or physician conflicts of interest that would negatively impact risk framing or data collection. Notice too that the patient-physician implementation requires educational components at the clinician level. Not all clinicians know how to

[10] Even if that trial data is held by regulatory bodies, it might still be unreleased to the public under 'trade secrets' (Lexchin 2016). This is problematic when public funds have contributed to that industry research (Langat et al. 2011).

[11] It should be noted that 'transparency' is not an unqualified good in participatory research (Quinn 2021).

report SADRs (Lopez-Gonzalez et al. 2009). Inman's 'sins' discussed earlier would also need exorcising to some degree. The 'buy-in' from clinicians that SADR reporting is part of their day-to-day practice stands in contrast to 'measurement fatigue', i.e., the fatigue that seemingly all aspects of clinical practice are being measured by health researchers with the aims of efficiency. There is also a perceived research-practice distinction that many practitioners hold onto – likely for the worse (Bluhm & Borgerson 2018) – but hold onto nonetheless. Changing the attitudes of clinicians, creating more time for them to do this SADR reporting with their patients, and education directed at Inman's 'sins' requires changing entrenched, institutional features of what many perceive the practice of medicine to be – no small feat. Along with these more 'pragmatic' challenges with the patient-physician approach, there are pragmatic challenges in the other approaches as well. Getting similar 'buy-in' from patients in the patient-dominant model, developing novel applications and technologies to track SADRs, addressing the legality of implementing such a system in the industry-led case, etc.

These are not all of the issues that can arise from thinking about our implementations of a contributory project aimed at mitigating underreporting from section 4. Nor are the examples in section 4 exhaustive of imagined instances. However, I think the discussion so far suffices to show that the kinds of issues that can arise in these contexts are of three kinds: bioethical issues/harms (e.g., harms from poor framing and nocebo effects, harms from data privacy violations), social-epistemic issues (e.g., the 'noise' caused by nocebo effects, industry biases and conflicts of interest, poor framing that continues underreporting), and pragmatic issues/constraints (e.g., 'buy-in,' mitigating Inman's 'sins', legal issues, creating/developing new technologies). Each of the imagined implementations faces these sorts of problems. There is no necessary connection between the imagined examples and the three types of problems that can arise. Intuitively, the industry-led approach will have more of an issue with industry bias than, say, the patient-physician approach, but not necessarily so. Having considered these problems with possible implementations of contributory participation directed at underreporting, we are now able to give an evaluative framework. To put it simply, suggestions to engage patients as contributors in order to mitigate underreporting that address or prevent the sorts of issues discussed will be preferable to those that do not. Or in other words, proposed implementations ought to fulfil the following criteria that constitute an evaluative framework:

(i) *Undue or preventable harms ought not befall patients/reporters.* E.g., poor data-privacy, nocebo effects from inappropriate risk framing.
(ii) *The social-epistemic aims of pharmacovigilance should not be hindered in collection, analysis, or distribution.* E.g., 'noise free' data collected, framing risks to not preclude reports, having accessible and transparent data maintaining privacy, accounting for or controlling industry bias.
(iii) *Proposals ought to account for existing practical constraints in clinical practice.* E.g., 'buy-in,' utilization of and issues with existing infrastructure and technologies.

There are likely various ways to 'meet' these criteria. Avoiding or mitigating nocebo effects in (i) and (ii) can be done through things like risk framing that does not cause negative expectations. Jeremy Howick (2020) highlights a case where two groups of patients were told about a risk occurring (a) 1 in 10 times or (b) not occurring in 90% of cases. Patients in group (a) experienced more SADRs than patients in group (b), even though the information is technically the same. Risk is also subjectively perceived, how one person considers it is different than others. There is no one-size-fits-all strategy here. This is difficult to do with things like mobile applications and public databases that are static, and something that may need to be considered with contemporary existing reporting infrastructures.

Addressing criterion (ii) could entail policies around transparency, public oversight, or other policies philosophers have suggested about mitigating industry biases (e.g., Biddle 2007; Biddle 2013). Thinking about the three criteria also gives some justification for why contributory participation is preferable to the other forms of participation presented by Shirk et al. (2012). Experts are involved in contributory participation, who may be the best ones to communicate risks fairly. Experts are in better positions to do the analysis of SADRs in a way trusted by regulatory bodies.[12] Experts and clinicians ideally also are free from things like industry biases or conflicts of interest, though this may not be the case. Also, given that the way reporting infrastructure is now already set up, a contributory approach is the most pragmatic and immediately instantiable, i.e., addressing (iii), of the forms of participation on offer for mitigating underreporting.

[12] Though this might be overly strict epistemically in some contexts (Kovaka 2021).

We might imagine a perfect society where there is adequate reporting, but this does not help us if concrete changes towards that ideal are not possible, or at least feasible. The creation of an app, the licensing of a government or public agency, broad educational interventions, etc. can be imagined solving these issues. However, solving the problem of underreporting begins with the tools and constraints we have now. Inman's 'sins' like lethargy are largely pragmatic. The best step forward to mitigate underreporting is likely the step we can take today, knowing what we know about practical constraints. We should not ignore the actual concrete conditions of modern science when talking about interventions and policies to increase the veracity of social-epistemic projects (Pinto 2015). Some approach might ideally fit the first two criteria but can fail at the third if institutions and clinicians reject the approach. The high associated costs in setting up programs and getting buy-in that solving underreporting is part of the day-to-day job of a clinician is not irrelevant. Criterion (iii) may entail taking small, productive steps given the resources we have at our disposal now and creating systems that are easy to 'buy-into.' Likely, what (iii) entails is that clinicians need to be an intrinsic part of creating proposals that would include patients in pharmacovigilance.

In sum, this framework allows us to answer the question of the paper more fully, i.e., is there a 'best' way for patients to participate in pharmacovigilance, especially considering mitigating underreporting? Recall that answering this required looking at both (1) what form of participation would be appropriate for such a task and (2) how we could evaluate better from worse proposals. In the preceding sections we saw that contributory participation was the most appropriate form of participation, answering (1). Now with an evaluative framework made explicit here, we have an answer to (2). With these considered, we have an answer to our question. If we are to include patients in pharmacovigilance with the aim of mitigating underreporting, the 'best' way to do it would be with patients primarily as contributors to projects or within policies that actively mitigate bioethical issues and harms like nocebo effects, are transparent and free from social-epistemic biases like industry biases that infringe on discovering and preventing drug harms, and that have 'buy-in' from health care professionals and the public while using existing or accessible methods. We might of course just take this as intuitive. However, what has been presented here could be considered a philosophical justification for such an intuition.

6. Limitations

An initial limitation here is what to do when two separate proposals might meet all three criteria; which ought we prefer? I think the answer to this requires knowing to what degree each criterion is met, or the degree of probable success the two suggested approaches will have in meeting the criteria. This would likely need to be done on a case-by-case and empirical basis. Thinking back to the abstract examples in section IV, we can think of each case modified to meet the three criteria. If an industry-led approach actively minimizes patient harms, communicates risks in a fair way, is transparent and open with data, that is a 'better' way to encourage patients to report SADRs to mitigate underreporting than a patient-physician approach that does not do the same. But if we had something like a proposed patient-physician approach that did meet the criteria and an industry-led approach that also met the criteria, what would the framework say? We might still be skeptical of a private-industry's attempts to meet criterion (ii), and so we might say the patient-physician approach we are comparing it with is better. But that does not mean we should halt this industry-led approach if resources allow. Note also that there may be other kinds of bioethical concerns than nocebo harm and patient privacy, and those would need to be accounted for in practice. The same would follow for social-epistemic and pragmatic concerns. Are there any criteria that outweigh each other? I think so. The bioethical criterion is the most important.[13] However, admittedly, if the second criterion is not met, it would not be clear pharmacovigilance was even occurring in the first place.

Large-scale change is needed if the problem of underreporting in pharmacovigilance is to be solved. These large-scale changes might be done with existing infrastructure – which is not without its own problems (Veronin et al. 2020; Getz et al. 2014) – but what seems to be at stake here is something social and institutional. Contemporary medicine is just not set up in a way where the aims of pharmacovigilance are maximized. However, though this integration should be done on epistemic or ethical grounds, getting it done on practical grounds is another story. Moreover, instantiating policies takes incentivization, and one must be careful that the core aims of pharmacovigilance in those cases are not overridden by the incentives. Criterion (iii) does not preclude new creations with which to solve underreporting, it merely prefers the use of existing resources. If new institutions or methods

[13] That this ought to be maintained even in research contexts is supported by policies like the World Medical Association's Declaration of Helsinki, stating that "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."

that enhance reporting come about, (iii) would automatically entail using these. Also, dealing with Inman's 'sins' would have to contend with (iii), especially in something like a patient-physician approach. Changing complacency, lethargy, diffidence, etc., require interventions on a large scale and buy-in from individual clinicians. Achieving this will require thinking about entrenched practical and institutional attitudes.[14] Navigating the complexity of any kind of real-world implementations of the kinds discussed here is precisely the purpose of criterion (iii).

7. Conclusion

Knowing what the 'best' way – if any – for patients to participate in pharmacovigilance with the aim of mitigating underreporting requires answering two related questions: (1) what would be the proper way for patients to participate in such a task and (2) how might we evaluate better from worse policies or suggestions for how to implement this. Question (1) was answered by surveying the different ways the public can participate in science and concluding that patients as *contributory* participants is the most appropriate role. Question (2) was answered by imagining the ways in which contributory projects or policies could go wrong. From considering how these go wrong, we developed an evaluative framework with which we could judge better from worse suggestions about patient inclusion to mitigate underreporting. This framework is composed of three criteria: (i) undue or preventable harms ought not befall patients, e.g., nocebo effects and violations of data privacy, (ii) the social-epistemic aims of pharmacovigilance ought not be hindered in data collection, analysis, or distribution, i.e., impacted by industry biases or conflicts of interest, and (iii) proposals ought to account for existing infrastructures and practical constraints in clinical practice, e.g., the 'buy-in' of health professionals and the public.[15]

[14] We might also imagine something like Inman's 'sins' as consequences of values held because of epistemic factors, e.g., epistemic risks (Due, manuscript).

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