COMMENTARY

Devil in the Details: Physician Duties and Expanded Access

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Abstract: Vermeulen et al. suggest a moral duty exists for physicians to inform patients of "relevant opportunities" for Expanded Access. Such a duty is likely both too broad, leading to important practical challenges, and too narrow, without further steps to promote patient access. However, physicians should be expected to be aware of the EA pathway, disclose it to eligible patients, and support the pursuit of EA options reasonably likely to help.

In FY19, the last pre-COVID year, the US Food and Drug Administration (FDA) reported receiving nearly 2,000 Expanded Access (EA) requests for investigational drugs and biologics outside clinical trials.[1] FDA almost always grants these requests, but this modest total is eclipsed by the number of seriously ill patients who reach the limits of approved therapies each year and who might be interested in pursuing unapproved treatment options. Some upstream drop-off in these numbers occurs when companies decline EA requests before they get to FDA, while another portion can be attributed to a key gatekeeper even earlier in the EA pathway: physicians.

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There is little systematic evidence about how often US physicians raise the option of pursuing EA with their patients. In a recent study of oncologists practicing at large, northeastern academic medical centers — a decidedly narrow sample, but one comprising well-resourced physicians with ample exposure to clinical trials and cutting-edge science — we found that most reported engaging in infrequent EA discussions, only about once or twice a year.[2] These oncologists noted that they were the ones typically initiating EA discussions, rather than patients or families. They also expressed a strong sense of caution, raising the prospect of EA only when convinced there was a valuable and realistic investigational drug to offer; sometimes they even confirmed that the relevant company would be willing to provide access before mentioning EA as a possibility to patients.[3]

Are these physicians violating their moral duties by failing to introduce EA more often and more fully including patients and families in decisions about whether to proceed down this pathway? In this issue of *JLME*, Vermeulen and colleagues suggest the answer might be yes.

Vermeulen et al. argue that although physicians have no definitive legal obligation to inform patients about "potentially relevant opportunities for expanded access to investigational drugs," they nonetheless bear a moral obligation to do so, rooted in their duties to promote beneficence, autonomy, and equity.[4] These are critical ethical issues that have not yet been adequately addressed in the growing EA literature, but the devil is in the details. In particular, the parameters of the proposed moral duty to inform need to be clarified. Also, it is unclear that a mere duty to inform without a duty to pursue, support, or provide EA will

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be meaningful to patients or effective at addressing equity concerns.

Legal Duties

Vermeulen et al. correctly conclude that patients will usually lack a legal claim against a physician who fails to disclose the possibility of EA. In the US, this would be handled as a malpractice case and would require the aggrieved patient to demonstrate that the physician violated their duty of informed consent and that this breach of duty caused the patient harm. As the authors note, the standard of required disclosure can be assessed in several different ways — from the perspective of a reasonable physician, a reasonable patient, or a particular patient — and US states differ in their approach.[5] Given that EA discussions seem to be rare, it is unlikely that a patient would be able to successfully argue that a reasonable physician would have disclosed EA. In a jurisdiction with a more patient-centric approach, even if a reasonable patient would have preferred disclosure, the claimant would also have to demonstrate harm by the physician's failure to do so. Considering that the products in question are only investigational, this could be a tall order.

In general, it is good policy to avoid legal obligations to disclose or offer unproven medical interventions, as this approach risks conflating physicians with vending machines rather than learned professionals with special expertise to inform patient care. The problems with this perspective have been made obvious during the COVID-19 pandemic, as some patients and families advocated strongly — and sometimes even sued — for access to unproven drugs such as ivermectin.[6] Patients are entitled to be informed of medical interventions backed by high-quality evidence supporting a conclusion that those interventions are reasonably likely to satisfy the patient's goals, but legal obligations should end there; decisions to offer unproven interventions that are nonetheless legally available and professionally acceptable should be left to physician discretion.[7] Importantly, even the federal Right to Try law (a pathway intended to be even more permissive than EA) seems to recognize this, specifically noting that "[n]o liability shall lie against a … prescriber … for its determination not to provide access to an eligible investigational drug[.]"[8]

Moral Duties

Since legal duties do not always overlap with moral duties, Vermeulen et al. assess the two possibilities separately, finding no principled argument against a moral duty to inform patients of "relevant opportunities" for EA, while recognizing several practical concerns. It is, of course, challenging to suggest that *relevant* opportunities should be withheld from patients — but what counts as a relevant? Should patients be informed of every investigational agent under study for their disease? Considering that US regulations do not even require that EA drugs have completed Phase I testing (which is needed to qualify for the Right to Try statute),[9] that could be overwhelming for both patients and physicians, depending on the extent of activity in a given disease area. It would surely be appropriate to limit disclosures to those EA options FDA is likely to permit, given the regulatory requirement that "potential patient benefit justifies the potential risks … [which] are not unreasonable in the context of the disease or condition to be treated[.]"[10] However, this is an extremely broad standard for patients facing death and may not narrow the field much. It would also be appropriate to limit disclosure expectations to those options a company is likely to allow, although that might inhibit a patient's ability to advocate for the company to take a different position.

Overall, any duty to inform patients of potential treatment options should reflect the strength of available evidence, getting stronger as investigational drugs proceed toward regulatory approval. But there are many open questions, including whether there should be some threshold of expected benefit, whether the possibility of psychological benefit should suffice even if improvement in the patient's physical status is unlikely, and whether a desire to "leave no stone unturned" is enough to trigger an informational duty, all issues raised by academic oncologists when describing how they make choices about when to offer EA.[11] Another question related to limits is whether this purported duty to inform would also call on physicians to ensure their patients are aware of treatment options available only in other jurisdictions, through EA or otherwise. As Vermeulen et al. acknowledge, there are substantial practical burdens to consider, not least of which is the challenge of making sure that physicians are themselves aware of relevant investigational options. Yet this must be more than an afterthought. We cannot specify moral duties without first determining that those duties would be practically achievable — ought implies can.

Information vs Access

Assuming appropriate limits are possible — which perhaps could be facilitated by replacing "relevant" in Vermeulen et al.'s formulation with "reasonable" opportunities, leaving added room for physician discretion regarding which EA options are to be disclosed — the next consideration becomes whether disclosure

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alone is enough. Should there be some further obligation to help a patient successfully access an investigational intervention through EA?

Disclosure is a first step toward promoting autonomy, beneficence, and equity and Vermeulen et al. are correct in noting that these goals cannot be achieved without making sure that patients are at least aware of their options. But neither can they be achieved if patients are unable to secure EA after learning of it. In fact, there is reason to suspect that a moral obligation limited to mere disclosure could exacerbate inequities in EA, as the most privileged patients will be in the best position to push through next steps once informed. Yet, given the many tasks associated with pursuing EA compared to more typical clinical care, any further expectation would impose a more substantial burden on physicians beyond the already significant challenges associated with simply staying up to date on investigational options. For example, physicians (and their staffs, if available) must handle requests to companies, which may necessitate some advocacy if the initial response is "no." They must also obtain institutional review board approval, ensure FDA sign-off, and maintain records and reports.[12] Additionally, they might be expected to potentially help resolve financial challenges, which sometimes arise for administration costs and other expenses regardless of whether the company provides the investigational EA drug free of charge.[13] Each of these steps could demand several hours of work against a backdrop of already harried clinical practices and potentially minimal institutional support. In the sense that time devoted to these matters cannot be spent in other ways, this is a zero-sum game, necessitating critical discussion of what resources should be devoted to supporting the chance of benefit through EA and what tradeoffs should be viewed as acceptable.[14]

Reasonable Expectations

Ultimately, a broad moral obligation on physicians to disclose — or to pursue — specific EA options likely asks too much. Instead, a weaker standard might nonetheless be an improvement over the status quo. Building on Vermeulen et al.'s proposal, physicians should be viewed as having moral obligations: (1) to be aware of the EA pathway; (2) to disclose the pathway's existence to patients who have exhausted their treatment options; and (3) to do their best with the resources they have available when it comes to identifying, equitably disclosing, and supporting the pursuit of EA options they deem reasonably likely to help, based on their expert knowledge and patient preferences. Although physician education should ensure that they have basic knowledge regarding this regulatory possibility, Vermeulen et al. would likely agree that it is not a moral failing for a busy physician to be unaware of every plausible investigational option or to be unable to support a patient's EA request in light of insufficient resources.

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Because EA treatments are not yet proven, they cannot appropriately be described as entitlements,[15] nor should failure to disclose be met with the same level of opprobrium as failure to disclose standard treatment options. Nonetheless, Vermeulen et al. are justified in arguing that more physician disclosure regarding EA would be a good thing, as it is unlikely that all patients who might be reasonable candidates for the pathway are currently taking advantage of it. The authors' recommendations regarding training, publicly available information about pharmaceutical company EA policies, and efforts to overcome misconceptions about barriers to EA are all steps in the right direction. Efforts directed to making sure that EA offers are not made only to the most privileged patients are especially important, as the authors note. Clearer guidelines to help clarify when clinicians should disclose EA options, which options they should disclose, and when they are justified in refraining from doing so could help improve consistency across physicians, although disparities in the institutional resources available to support EA will likely remain — as they do in all areas of the US health care system.

Although not mutually exclusive to EA, given the requirement that trial participation be unavailable

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to patients seeking to use that pathway, there is one more critical physician obligation to patients who have exhausted approved treatment options — one that should receive far more attention than it has. Physicians should help identify and then encourage patients to participate in trials for which they are eligible. This approach can both promote access to potentially beneficial investigational treatments for patients today and generate knowledge to prospectively inform the standard of care for patients tomorrow.

Note

The author has no conflicts of interest to disclose.

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