low dose of andexanet costs $24,000, which is the dose 85% of the patients in the trial received. Essentially, the only patients who received a high dose ($48,000) were those who received higher doses of factor Xa inhibitors less than 8 hours before andexanet dosing. Andexanet is by no means cheap, but calling it a $50,000 drug is misleading. Cost-effectiveness and number needed to treat are problematic to calculate without control groups for both andexanet and prothrombin complex concentrate. But this should not conflate the evidence for efficacy alone. Andexanet has a reasonable mechanism and underlying hypothesis by stoichiometrically sequestering the factor Xa inhibitor drug, allowing native factor Xa to function in the clotting cascade. It has an extensive preclinical program, including several animal models and hundreds of healthy and older adults. It has a prospective cohort study with well-defined outcomes in 352 patients with major bleeding, with academic oversight and adjudication of safety and efficacy and regulatory oversight. It has Food and Drug Administration and European Medicines Agency approval, and a randomized trial is in progress to address potential uncertainties in benefit:risk. Prothrombin complex concentrate makers have not embarked on this lengthy and costly path, and we will probably never know whether prothrombin complex concentrate is either safe or effective.

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FDA Approval of Andexanet Alfa Based on a Single-Arm Trial: If There Is a Villain, Who Is It?

To the Editor:

A recent *Annals* Journal Club piece critiqued ANNEXA-4, sponsored by Portola Pharmaceuticals, the manufacturer of andexanet, arguing that it was unethical to conduct a single-arm trial, and that a placebo-controlled design should have been used.[1,2] I was a coauthor on the critiqued article and chaired the sponsor's Medical Advisory Panel that preceded Food and Drug Administration (FDA) approval and the drug's launch, for pay.

The Journal Club piece suggests that something nefarious is afoot in the commercialization of andexanet. If so, who's the villain? People use "structural violence" to refer to harm from social structures, rather than ill intent of individuals. "Structural violence is one way of describing social arrangements that put individuals and populations in harm's way," said Paul Farmer.[3] I suggest that we are dealing with a "structural" problem in drug development.

Pharmaceutical companies have a duty to patients, but their first duty is to their shareholders. (No, I don't own stock in Portola.) In our capitalist society, most new drugs are created by pharma, not academia or government. Without pharma, the meme goes, we would have few new drugs because of National Institutes of Health funding priorities and the cost of pivotal trials (ANNEXA-4 ran well into the 9 figures).

Adam Smith[4] envisioned a system of enlightened capitalism, in which self-interest was tempered by an interest in the public good. As capitalism has unfolded in the United States, there has been more emphasis on self-interest than enlightenment. But the FDA, the Code of Federal Regulations (empowers institutional review boards), and, more recently, ClinicalTrials.gov, do counterbalance industry's self-interest.

If there is something wrong in the development of andexanet, who's to blame? If you were a pharmaceutical company, with a primary duty to your shareholders, would you pass up the opportunity to get a drug approved in a single-arm trial with an *in vitro* main outcome (decrease in factor Xa activity)? Nope. The blame here rests with the FDA.

All this talk about a placebo-controlled trial is silly. Andexanet should have been compared head-to-head with prothrombin complex concentrate. Andexanet works by sequestering the anticoagulant for a few hours so a clot can form. Roughly 2 andexanet molecules are infused for every molecule of inhibitor. A hematologist friend of mine once calculated that a dose of prothrombin complex concentrate has as much factor Xa as 16 bags of fresh frozen plasma. Here's the question that shows that the emperor (the FDA) has no clothes: why didn't somebody calculate the dose of prothrombin complex concentrate needed to bypass the inhibitor, and mandate a trial that randomized participants to andexanet versus that dose of prothrombin complex concentrate? In 2018, Schulman showed that, of patients with Xa-inhibitor-associated major bleeding, 65% had effective hemostasis after *a fixed, low dose* of prothrombin complex concentrate (2,000 units) (95% confidence interval 53% to 77%),[5] versus 79% in ANNEXA-4 (95% confidence interval 64% to 89%). When ANNEXA-4 was designed, this should have been foreseen. The people at Portola are smart. Should they have designed a comparative trial? Nope. How could they? It would have been a betrayal of Portola's duty to its shareholders. What about the very smart people at McMaster University, who designed the trial? Interesting question. One could also argue that institutional review boards worldwide were at fault for not objecting to the nonuse of prothrombin complex concentrate as a comparator, but that's another interesting question.

But the FDA should have known, and should have mandated a comparative trial, *with a patient-centered outcome* (effective hemostasis, Rankin Scale score, or mortality). A finding of superiority would have been unlikely. If the FDA had done this, where would we be today? Given the expense of manufacturing andexanet, its commercialization might have been abandoned. At a minimum, Portola would have been forced to sell andexanet for less to compete with prothrombin complex concentrate.

The naked emperor has now mandated that Portola conduct a randomized trial of andexanet versus "the available standard of care."[6] Really? Why not a specified dose of prothrombin complex concentrate? There *is* no "standard of care" for reversal of factor Xa inhibition, and this language leaves open the possibility that many patients randomized to the standard of care arm will receive inadequate therapy, biasing the trial in favor of andexanet.

By the way, the FDA and others have wrongly paid a great deal of attention to the high rate of thromboembolic events among ANNEXA-4 patients. Andexanet has no procoagulant activity. In Phase 1 studies, normal volunteers receiving it had no thromboembolic events. ANNEXA-4 participants had thromboembolic events because they had a clotting diathesis to start with, and spent weeks in bed recovering. The International Society of Thrombosis and Hemostasis and others are responsible for failing to figure out when such patients should be reanticoagulated after hemostasis is attained.

But clinicians just want to know how to care for patients. The quandry is particularly poignant in light of the fact that manufacturing difficulties initially prevented Portola from distributing andexanet widely. Here's the answer: if a patient receiving a factor Xa inhibitor has a major hemorrhage, and andexanet is not available, you should give a high dose of prothrombin complex concentrate (eg, 5,000 units). And consider giving tranexamic acid too (not evidence based, but safe and cheap).

If andexanet is available in your hospital, use it—for patients who have insurance that will pay for it (for those who don't…interesting question).

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In reply:

We appreciate the responses to our Journal Club[1] article by Drs. Milling and Connolly, and by Dr. Pallin. Publications in this section of *Annals* are intended to be succinct and broadly educational; it is not always possible to delve into the nuances and details of a topic. In response to Drs. Milling and Connolly's concerns, we regret any personal offense members of the study team may have felt by our mention of the ethical considerations of single-arm studies. Our point was that in this rapidly shifting field, equipoise should be assessed not only at trial inception but also continuously as new and alternative treatments emerge.[2]

Dr. Pallin's thoughtful comments highlight the challenges of drug development, Food and Drug Administration oversight, and the implications for the comparative clinical trial design. We, too, agree that postpublication peer review is necessary to help protect patients.

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Inhalational Methanol Intoxication: Emerging Issues in the Netherlands Resulting From Illegal Drug Production

To the Editor:

Inhalational methanol intoxications are rare. However, since 2018, the Dutch Poisons Information Center has been increasingly contacted for information requests and treatment advice concerning patients who developed severe symptoms caused by methanol inhalation while working in an illegal drug-manufacturing laboratory. In this communication, we report 3 cases.

A 28-year-old man arrived home with general complaints after "a night out." The next morning, he was found unresponsive and transported to a hospital. On arrival, he presented with coma (Glasgow Coma Scale [GCS] score 3), apnea, hypertension (blood pressure 166/78 mm Hg), tachycardia (pulse rate 129 beats/min), and fixed dilated pupils. Laboratory examination showed metabolic acidosis (pH 6.31; lactate level 21.7 mmol/L) with high anion gap (46.9 mmol/L) and osmolal gap (108 mmol/L). Approximately 8 hours later, 2 relatives (men aged 26 and 20 years) arrived at the hospital. They both felt ill, but were fully conscious (GCS scores 14 and 15). Laboratory results showed metabolic acidosis (pH 7.1 and 7.2) with an increased anion gap (39.6 and 22 mmol/L) and osmolal gap (54 and 41 mmol/L). One of the patients admitted working in an ecstasy (methyleendioxymethamfetamine) laboratory for greater than 40 consecutive hours more than 24 hours before admission. Considering the differential diagnosis of a metabolic acidosis with high anion and osmolal gap,