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Abstract

Medication-use evaluations are meant to ensure that medication-use processes are consistent with prevailing standards of care, assure optimal use of therapy, and reduce the risk of medication-related problems. Reversal agents for direct oral anticoagulants are a worthy focus for medication-use evaluations for reasons of efficacy, safety, and cost. A multidisciplinary team of experts developed 2 medication-use evaluation templates illustrating the application of professional society guidelines to the appropriate use of andexanet alfa.

Keywords

andexanet alfa, medication review, anticoagulant reversal agents, hemorrhage, intracranial hemorrhages

Background

One of the US FDA's primary charges is the process of medication approval wherein a multidisciplinary team of experts weighs evidence of benefit vs risk in the treatment of specific health conditions. There is growing awareness of discordance, however, between outcomes observed in tightly controlled clinical trials vs those from the real-world setting, where health care providers often must contend with patients who often do not conform to strictly defined trial inclusion criteria. Sometimes this gap is addressed through the evaluation of newly published evidence and consensus guidelines developed by a group of experts. Despite these efforts, health care providers sometimes utilize medications for indications or in situations where evidence is limited or the benefit is not clear. While the decision to deviate from the evidence may seem well-reasoned, these variances should be evaluated for efficacy, safety, or cost outcomes relative to prevailing standards of care.

A medication use evaluation (MUE) is a performance improvement tool aimed at improving therapeutic or process outcomes. The objectives of a MUE include: ensuring medication use practice comports with existing standards of care,

improving optimal use of therapy, and reducing medication-related problems.¹

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Recently updated guidelines for MUE development outline prioritization of medications meriting evaluation and delineation of ways a MUE's stated objectives may be incorporated into a quality improvement framework. The guidelines recommend using the FOCUS-PDCA model, which involves identifying a process to target and constituting a team of experts qualified to outline what is presently known about the process and causes of variation within it. The model then describes initiating a continuous cycle of designing a change, analyzing the results of enacting it, modifying the process to yield improved results, and then beginning the cycle anew.¹

Reasonable foci for a MUE include medications associated with significant or numerous adverse outcomes or those that incur a significant cost, both of which make antithrombotic reversal agents natural targets. Interest in real-world experience and institutional policies governing the use of antithrombotic agents spans decades^{2,3} due to the risk of catastrophic outcomes associated with the medication class.⁴ Commensurate with changes in prescribing practice, attention has begun to focus on direct oral anticoagulants (DOAC), the factor Xa inhibitors (FXais) in particular. Warfarin use has dropped 39% in US Medicare and Medicaid beneficiaries over recent years, while apixaban and rivaroxaban now account for 46% of oral anticoagulants prescribed.⁵ The risk of clinically important bleeding-related outcomes with oral FXais may compare favorably with those of warfarin in non-valvular atrial fibrillation (AF) or venous thromboembolism,^{6,7} but 2 to 5 DOAC-treated patients with AF per 1000 experience intracranial hemorrhage (ICH) annually,⁸ and major gastrointestinal bleeding occurs at an annual rate of 0.76%.⁹ Case-fatality rates in DOAC-associated major bleeding are 8% to 15%,¹⁰ and related hospitalization costs run into the tens of thousands of dollars.¹¹

The literature focusing on the real-world use, outcomes, and costs of DOAC reversal agents is more limited. Andexanet alfa was approved by the FDA in 2018 for reversal of anticoagulation in patients treated with rivaroxaban or apixaban who are experiencing uncontrolled or life-threatening bleeding. Prior to its approval, clinicians managed FXai-associated major bleeding with packed red blood cells, fresh frozen plasma, or prothrombin complex concentrate (PCC),^{12,13} and they continue to use these products off-label for the same indication today.¹⁴

Two leading quality assurance and patient safety organizations—the Joint Commission and the Institute for Safe Medication Practices—direct health systems to make anticoagulant reversal agents readily available and develop evidence-based protocols governing their use.^{15,16} Several professional society guidelines and expert panels, such as those from the American College of Cardiology, American Heart Association, and Anticoagulation Forum, favor using a specific reversal agent over a non-specific pro-hemostatic agent for reversal of DOAC-associated major or life-threatening bleeding when available.^{17–20} However, a recent evaluation of US hospitals providing emergency care shows

that fewer than 12% carry andexanet alfa compared to 60% with idarucizumab for reversal of anticoagulation in dabigatran-related bleeding,²¹ despite dabigatran's accounting for a small fraction of oral anticoagulants prescribed in the US.⁵ Another survey found 66% percent of hospitals that had not added andexanet alfa to formulary cited cost as a reason.¹⁹

Ongoing questions about the balance of andexanet alfa's efficacy relative to non-specific pro-hemostatic agents, safety, and cost^{12,14,19} make andexanet alfa an ideal drug for targeted MUE. To address practical considerations around appropriate use of andexanet alfa, the authors of this paper—a team of pharmacists and physicians who practice in emergency medicine, hematology, and antithrombosis stewardship—formed a multidisciplinary Advisory Panel (AP) that also included a finance representative and represented institutions with and without andexanet alfa on formulary.

As a MUE is an institution-specific performance improvement tool and the AP's members represented several different health systems across the country, the panel did not conduct a MUE directly. Rather, during 9 meetings over the course of a 4-month period, the committee developed 2 separate MUE templates each addressing a different step of the medication-use process. The AP chose the prescribing step for 1 MUE and dispensing for the other, weighing factors that included the relative priority of health-system needs relating to each step and an interest in illustrating the MUE planning process to the broadest possible audiences: prescribing for clinical staff and dispensing for those involved in the medication distribution process (eg, pharmacy staff). The AP also created a resource guide²² meant to provide customizable, turnkey templates that may be adapted by health systems locally during MUE implementation.

Medication Use Domains

Approach, Areas of Focus, and Rationale

The first steps in the process are to identify a process to target (Focus) and develop a team of experts to spearhead the MUE (Organize). The AP prioritized several potential objectives, outcomes, questions, stakeholders affected, and metrics to measure change. It placed emphasis on developing MUE templates that could be adopted by organizations of different sizes, recognizing some metrics are more the province of clinical studies than routine practice. The next step was to outline what is presently known about the process (Clarify). One approach the AP suggested in an implementation guide it developed is mapping out the steps of the medication-use process in a flowchart with decision nodes and sources of process variation (Figure 1).

To be successful, a MUE must provide actionable information. Once a health system collects data, those conducting the MUE must assess causes of process variation (Understand) and develop proposed changes to targeted causes of process variation (Select). The AP categorizes several groups of

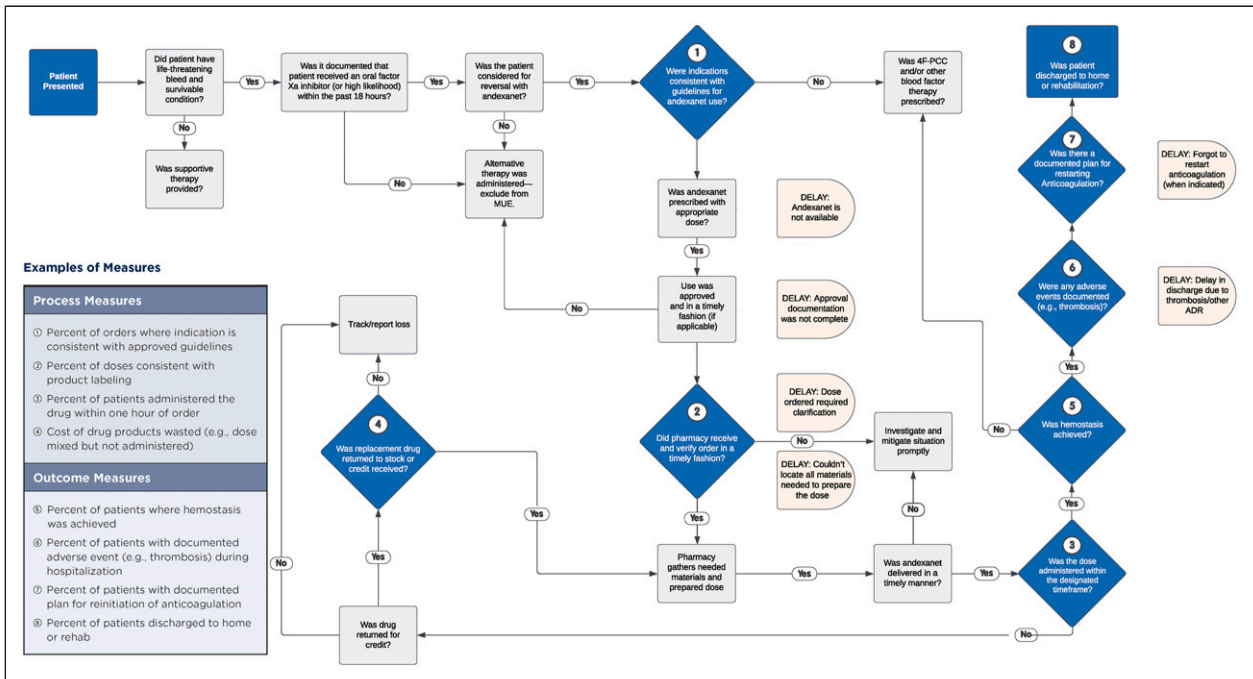


Figure 1. Medication-use evaluation process flowchart: direct oral anticoagulant reversal agents^a.

^a**Abbreviations:** 4-FPCC, 4-factor prothrombin complex concentrate; ADR, adverse drug reaction; MUE, medication-use evaluation.

practical data types in each of its templates. Factors the AP includes in its prescribing MUE template are whether practice is consistent with professional guidelines and prescribing information and identification of the best candidates and strategies for anticoagulant reversal. In the dispensing-related template, elements include whether an institution considers andexanet alfa acceptable in a patient who has already received PCC, appropriate dose verification, and time to administration. Tables 1 and 2 show the prescribing and dispensing MUE templates the AP developed, respectively.

Enacting Process Improvement

The latter half of the FOCUS-PDCA model outlines incorporating a MUE's findings into a cycle of quality improvement to address causes of variation. Questions concerning andexanet alfa use might include:

- ❖ Has an institution discovered through its MUE process that inappropriate patient candidates were selected for reversal? Potential solutions:
 - Order sets can be built to include prompts for required criteria (eg, imaging tests)
 - Expert panels emphasize the importance of clinical decision support tools and standardized electronic order sets embedded with the most up-to-date evidence to identify the best candidates and strategies for anticoagulant reversal^{18,19} (eg, Glasgow coma scale, ICH score)

- ❖ Has an institution discovered through its MUE process that incorrect doses of andexanet alfa have been administered or that it has been lost in storage or transit? Potential solutions:
 - Box kits for preparation by the nurse or pharmacist at the bedside, as has been done with other reversal agents¹⁹
 - Inventory control measures (eg, RFI technology) or a strong process in place to ensure the medication is returned if not administered.

Considerations and Limitations

A MUE has its share of limitations. It is a tool to identify process variation, design solutions, and measure change. While a well-designed MUE may fulfill the need for real-world data, unlike clinical trials, most MUEs are not designed to establish causality, and, therefore, caution must be used when interpreting and extrapolating the results. For example, the templates developed during this project were not designed to measure factors like the extent to which a reversal agent impacted a patient's clinical course relative to the patient's baseline prognostic status, optimal provision of supportive care measures like blood pressure management, and impacts of delays in reinitiating anticoagulation therapy.

Manual chart review should be minimized, as it is time-consuming, resource-intensive, and prone to errors of omission and transcription. MUE guidelines therefore recommend automating

Table 1. MUE Template: Prescribing Process. Medication-Use Question #1: Is Prescribing of Andexanet Alfa Consistent With Approved Guidelines?^{a,b,c}

MUE Criteria

FXa Inhibitor Reversal: Focus on Andexanet Alfa

- The following factors were considered when weighing the decision to use andexanet alfa:
 - Confident the patient was taking an oral FXa inhibitor
 - Confirmation of major bleeding (ie, a decrease of ≥ 2 g/dL of Hgb and/or administration of ≥ 2 units of RBCs)
 - Determination of whether bleeding was critical (ie, critical site bleed or life-threatening)^d
 - Determination of whether this was a salvageable condition (for example, if ICH consult stroke neurologist or neurosurgeon who will determine salvageability [eg, consider cutoffs for GCS and ICH scores and ICH volume consistent with the ANNEXA-4 trial])
 - Collateral issues weighed (eg, renal insufficiency, reversal management for concomitant aspirin or other antiplatelet agents, time since incident occurred, what was given at outside hospital for reversal)
 - Patient met or exceeded threshold FXa inhibitor plasma level (eg, ≥ 50 ng/mL for major bleeding and >30 ng/mL for an invasive procedure with high bleeding risk)^e
 - Identification of specific clinical inputs obtained before deciding to treat
- Prescribing is consistent with institution's approved guidelines
 - Andexanet alfa may be used for urgent reversal of anticoagulation when there is:
 - Known ingestion of an oral FXa inhibitor within an 18-hr window
 - Potentially critical site or life-threatening bleeding, including salvageable intracranial hemorrhage; gastro-intestinal bleeding; or acute, symptomatic bleeding in a critical organ (eg, pulmonary hemorrhage, retroperitoneal, intra-articular or pericardial, intracranial, intraspinal or intramuscular with compartment syndrome)
 - Failure to reverse FXa inhibition is likely to result in death or permanent disability
 - Reversal is required in the setting of bleeding to safely perform emergent surgery
 - Has potentially critical site or life-threatening bleeding that was refractory to other reversal strategies
- Applicable clinical tests and monitoring initiated
 - Laboratory tests
 - CBC
 - Hepatic function
 - Renal function
 - PT, aPTT, anti-FXa assays^e
 - For critical site bleeding
 - Serial imaging tests (eg, for ICH, CT scan at baseline, 6 hours, and 24 hours for patients with a GCS score <13)
 - Other relevant consults are obtained, as applicable (eg, neurology/neurosurgery)
 - GCS is calculated, if applicable
 - ICH score is calculated, if applicable
 - For GI bleeding
 - Gastroenterology consult is obtained

^a**Abbreviations:** aPTT, activated partial thromboplastin time; CBCs, complete blood counts; CT, computed tomography; EHR, electronic health record; FXa, factor Xa; GI, gastrointestinal; GCS, Glasgow coma score; Hgb, hemoglobin; ICH, intracranial hemorrhage; MUE, medication-use evaluation; MRI, magnetic resonance imaging; PT, prothrombin time; RBCs, red blood cells.

^bThis is an example set of MUE criteria. Each institution should establish guidelines and MUE criteria appropriate to the setting.

^cThe MUE template and guidelines assume that andexanet alfa is available for administration.

^dFor assessment of bleeding and definition of life-threatening bleeding, see: Tomaselli GF, Mahaffey KW, Cuker A, et al, 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2020;76 (5):594-622. doi:10.1016/j.jacc.2020.04.053.

^eAssays specific for apixaban and rivaroxaban quantitation are specialized and are not widely available. Assays that are calibrated for each agent may not be available or the results reported in a time period that is useful in treatment decisions. For additional information, see: Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2016;14:623-7.

the data collection process as much as possible.¹ The AP's resource guide²² provides a sample data collection framework.

Finally, those conducting MUEs may encounter several barriers, including a failure to: engage experts in the areas affected; use consistent sources of data; obtain baseline

measurements; or follow through with a continuous cycle of change and further analysis that the changes have resulted in an improvement. The MUE guidelines and AP resource guide provide potential solutions to those and other barriers to the effective execution of an MUE.¹

Table 2. MUE Template: Dispensing Process. Medication-Use Question #2: Has the Pharmacy Implemented Processes to Ensure Safe and Cost-Effective Use of Andexanet Alfa?^{a,b,c}

MUE Criteria

FXa Inhibitor Reversal: Focus on Andexanet Alfa

- Order had all required elements
 - Anticoagulant to be reversed was an oral FXa inhibitor
 - Strength of last dose (or stated as unknown)
 - Timing of last dose or if unknown
 - Andexanet alfa dose (high or low) is correct
- Key elements for consideration are documented in the EHR
 - Indication (eg, life-threatening or uncontrolled bleeding or need for emergent surgery in the setting of bleeding)
 - Receipt of other factor product (if administered), dose and time of administration (including if at an outside facility)
 - Risk/benefit of reversal is assessed (eg, high thromboembolic risk)
- Approval process was timely
 - Required clinical information is documented in the EHR/date, time
 - Indication confirmed/documentated in EHR/date, time
 - Approval confirmed (if applicable)/date, time, and name of individual approving
 - Order date/time
 - Preparing pharmacist notified/time of notification
- Pharmacy/sterile products was alerted “stat”
 - The pharmacist verified the appropriate dose
 - Dose was prepared and delivered by pharmacist or pharmacy technician to the nurse
 - Dose was dispensed/date, time
- Prescribed dose was administered in a timely fashion
 - After reconstitution by the pharmacy, andexanet alfa stored at room temperature was used within 8 hr or 3 hr if prepared at bedside.
 - Bolus dose administered, then, within 2 min following the bolus dose, continuous IV infusion at a rate of 30 mg/min was administered.
 - End time for infusion documented.
 - At completion of the infusion, line flushed using a 50-mL bag of 0.9% sodium chloride to ensure that the entire dose was administered.
 - If they occurred after start of andexanet alfa, any arterial and venous thromboembolic events, ischemic events, and cardiac arrest were noted in EHR.

^a**Abbreviations:** EHR, electronic health record; FXa, factor Xa; MUE, medication-use evaluation.

^bThis is an example set of MUE criteria; each institution should establish guidelines and MUE criteria (eg, parameters for timeliness) appropriate to the setting.

^cThe MUE template and guidelines assume that andexanet alfa is available for administration.

Summary

A multidisciplinary team of experts developed 2 MUE templates illustrating the application of MUE guidelines to the appropriate use of andexanet alfa to serve as a customizable model for health systems interested in evaluating the same question or other medication-use processes locally.

Author’s Note

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Author Contributions

The following authors reviewed and provided feedback on the manuscript and actively contributed on the advisory panel that developed the medication use evaluations (MUEs) and its implementation guide: Drs. Burnett, Fanikos, Grandoni, Pollack, Rose, Spinler, and Streiff. Dr Fera served as project manager for the advisory panel, prepared the initial drafts of the MUEs and its implementation guide, and incorporated the advisory panel’s feedback into the submitted drafts of each. Ms. Moore actively contributed on the advisory panel in the development of the MUEs and its associated implementation guide. Dr Nussbaum facilitated advisory panel meetings with Dr Fera and reviewed and provided feedback on drafts of the manuscript, MUEs, and implementation guide. Dr Turck prepared the initial draft of the manuscript, incorporated the advisory panel’s feedback into the submitted draft, and reviewed and provided feedback on drafts of the MUEs and implementation guide.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Fanikos reports paid compensation for work on advisory boards for Boehringer Ingelheim International and Vifor, Inc. Dr Fera has received compensation from ASHP for contract work. Drs. Grandoni and Streiff report paid compensation for work on advisory boards for Pfizer Inc. Dr Nussbaum is an employee of the ASHP Foundation. Dr Pollack has received payment for consulting work with AstraZeneca, eXlthera Pharma, PhaseBio Pharma, and Provepharm. All authors report having received honoraria for participating in the meetings whose discussions formed the basis of this manuscript, which was funded by Alexion Pharmaceuticals, Inc. The authors declare no other potential conflicts of interest.

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