



Andexanet Alfa in the Management of Life-Threatening Bleeds in Patients on Direct Factor Xa-Inhibitors

Background

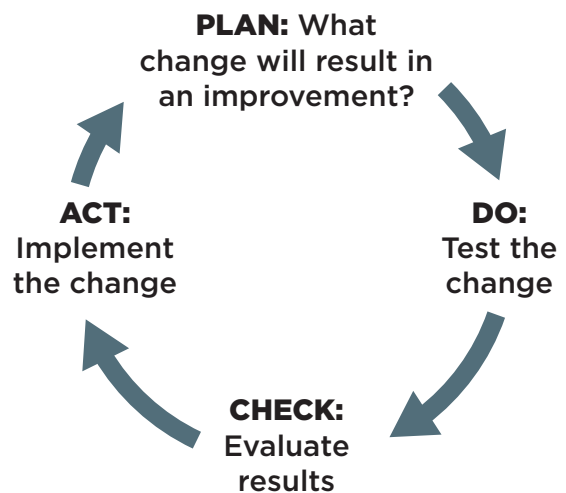
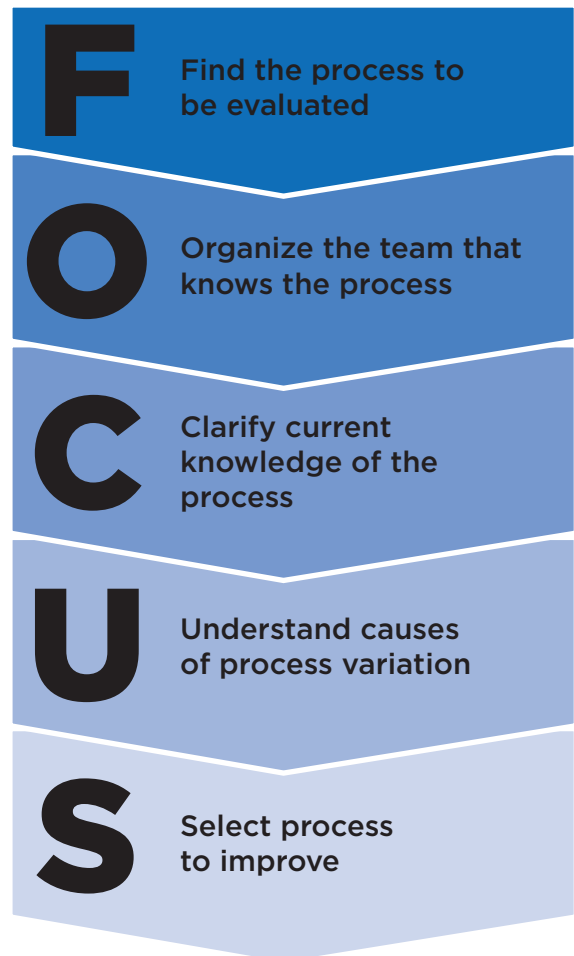
The American Society of Health-System Pharmacists (ASHP) recently published guidelines for performing Medication-Use Evaluations (MUE).¹ The ASHP guidelines define MUE as a systematic and interdisciplinary performance improvement method with an overarching goal of optimizing patient outcomes via ongoing evaluation and improvement of medication utilization. The guidelines also establish a process for identifying and completing an MUE while incorporating the roles and responsibilities of the interdisciplinary team. The elements of conducting an MUE include:

- establishing the goals and objectives of the MUE and defining the specific “research” or “medication use” question to be answered
- prioritizing and selecting the medication(s) and processes for evaluation
- establishing the ideal or current steps in the process
- defining measures to evaluate the process
- creating a process for data collection

An MUE process can focus on a clinical decision-making process (e.g., clinical guidelines for prescribing and the approval process) or a workflow process (e.g., ordering, preparing, dispensing, or monitoring the drug).

As a performance improvement tool, MUEs can be used when there is uncertainty regarding whether a medication is achieving its intended outcomes, is safe, or is being prescribed according to accepted guidelines. One model that can be applied is the FOCUS-PDCA model framework described in the ASHP guidelines (Figure 1). MUEs can also be part of a structured or mandated multidisciplinary quality management program that focuses on evaluating a medication’s overall value (including its place within a treatment guideline), cost-effectiveness, or improving patient safety.

Figure 1. Elements of the FOCUS-PDCA MUE framework



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Introduction

The ASHP Foundation facilitated the creation of this resource guide with input from an Advisory Panel (AP) of experts. This guide describes the application of the FOCUS-PDCA framework as a simulated MUE process improvement and the creation of an MUE template for the use of andexanet alfa (“andexanet”), a specific reversal agent used to manage life-threatening bleeding in patients who have been taking direct oral factor Xa inhibitors (DOACs). The widespread use of DOACs, the availability of national guidelines for the reversal of anticoagulation and management of life-threatening bleeding, the significant morbidity and mortality related to significant bleeding, the need for timely administration of reversal agents, the high cost of therapy, and the ongoing clinical debate about its place in therapy make andexanet an ideal drug for a targeted MUE. While this example is specific to an anticoagulant reversal agent, one can apply the framework described for conducting an MUE and adapt the template to other drugs and clinical scenarios.

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Applying the FOCUS-PDCA Framework

Find the process to be targeted for improvement.

The first step in conducting an MUE is to determine the indicator(s) for conducting the review, the process to be targeted for improvement, and the medication use question to be answered.¹ Several indicators can trigger opportunities for conducting MUEs, such as changes to the formulary, delayed medication delivery, adverse events reported, evidence of waste, cost constraints, or other concerns (Table 1).

When there are existing, approved guidelines in place, prescribing is a common process targeted for improvement (e.g., adherence to guidelines and formulary compliance). A group of local organization experts should be assembled to identify or determine the most relevant processes to review and primary indicators of the need to conduct an MUE. After much deliberation, the AP (our group of experts convened for this simulation) decided to focus on two key processes integral to managing life-threatening bleeding in patients taking factor Xa inhibitors: prescribing and dispensing the reversal agent andexanet.

Table 1. Indicators of need for MUE at different steps in the medication-use process¹

Step	Indicator
Prescribing	<ul style="list-style-type: none"> • Publication of guidelines that may change treatment patterns • New organizational interventions to improve medication therapy, such as changes to protocols or formularies • Changes to pharmacy clinical services to improve medication therapy • Introduction of or changes in quality indicators
Dispensing	<ul style="list-style-type: none"> • Signs of process failures, such as wasted medication or delayed medication delivery • Incorrect medication preparation • Dosing that requires clinician preparation or compounding • Ensuring compliance with regulatory requirements (e.g., Joint Commission, FDA, USP)
Administration	<ul style="list-style-type: none"> • Medication misadventures related to medication delivery systems • Multiple medication concentrations, units of measure, or infusion rates
Monitoring	<ul style="list-style-type: none"> • Adverse events, including medication errors, preventable adverse drug reactions, and toxicity • Signs of treatment failures • Patient/family dissatisfaction or deterioration of the quality of life attributable to drug therapy
Systems Management and Control	<ul style="list-style-type: none"> • Risk Evaluation Mitigation (REMS) programs, restricted distributions channels, or other access challenges • Drug shortages requiring replacement or therapeutic substitution • Timeliness of administration • Diversion of medications and materials • Lack of standardization or confusion within the medication-use process • Changes in contracts, cost, or spending on drugs • Organizational priorities such as budget constraints or cost saving initiatives

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Selecting the Medication-Use Question

The Food and Drug Administration (FDA) approved andexanet for use in adults treated with direct oral anticoagulants (DOACs), specifically, factor Xa inhibitors rivaroxaban or apixaban, when reversal of anticoagulation is needed due to major (i.e., life-threatening or uncontrolled) bleeding.² DOAC-related major bleeding is associated with significant morbidity and mortality and high cost of care. The average hospitalization cost for patients with intracranial hemorrhage (ICH) was estimated to be \$58,169 higher than those without bleeding, and the total all-cause healthcare costs during the following 12 months were significantly higher as well.³ Before andexanet approval, options for managing major bleeding included blood products, such as (red blood cells, fresh frozen plasma), 3- and 4-factor prothrombin complex concentrates (PCC), and/or activated prothrombin complex concentrates (aPCC).⁴⁻¹¹ Based on their practice experience, the AP agreed that DOAC reversal agents are generally indicated when:

- There is known ingestion of apixaban or rivaroxaban within an 18-hour window, and
- there is potentially life-threatening bleeding; including intracranial hemorrhage; gastrointestinal bleeding; or acute, symptomatic bleeding in a critical organ (e.g., pulmonary hemorrhage, retroperitoneal, intra-articular or pericardial, intracranial, intraspinal or intramuscular with compartment syndrome), and
- failure to reverse factor Xa inhibition is likely to result in death or permanent disability, or
- reversal is required to perform emergency surgery safely.

Despite andexanet's availability as the sole FDA-approved agent for reversal of factor

Xa inhibitors and support for its use in national guidelines, a recent evaluation of hospitals in the United States (US) providing emergency care suggested that only about 10% of hospitals have andexanet available for use.^{12,13} This is partly due to controversy that has emerged surrounding andexanet's place in therapy, including optimizing its efficacy, safety, and cost-benefit relative to alternate therapies.

This simulated MUE is designed to answer the two identified questions:

MUE Question #1: Is prescribing andexanet consistent with the institution's approved guidelines?

MUE Question #2: Has the pharmacy implemented processes to ensure safe and cost-effective use of andexanet?



TIPS AND STRATEGIES: Find the Process and Select the MUE Question(s)

- Identify processes based on indicators of need: improve safety, promote optimal therapy, standardize to reduce process variation, cost-benefit, and meet compliance standards.
- Select high-impact steps of the medication-use process: prescribing, dispensing, administration, monitoring, and systems management and controls.
- Seek input from all process stakeholders to develop the MUE question and prioritize efforts.

Organize the team that knows the process.

While product labeling lists approved indications and specific guidelines for dosing, the evaluation must consider new studies and updated clinical guidelines, changes in the cost-benefit equation and reimbursement (e.g., add-on technology payment), and the drug’s place in therapy. An institutional multidisciplinary advisory committee should be convened prior to initiating the MUE and have the expertise to:

1. confirm or update the approved guidelines
2. identify or refine key processes to assess and questions to be answered
3. select measurable objectives
4. assist in identifying references (e.g., recently published studies and guidelines)
5. design the MUE by deciding on methodology and selecting the sample population, sample size, and inclusion and exclusion criteria
6. create a data collection plan
7. review results and make recommendations for improvement¹

For this simulation, the external members of the AP (team) were selected because of their expertise in anticoagulation and management of anticoagulant-associated life-threatening bleeding. Members include prescribers (emergency medicine, hematology), pharmacists, and a representative from health-system finance. Some of the resources and references provided by the team as a basis for the evidence and discussion for this MUE are listed in Appendix E.



TIPS AND STRATEGIES: Organize the Team

- Consider all key stakeholders and the different perspectives they can bring or how they can support the evaluation.
- Consider approved labeling, build upon current consensus guidelines, review new literature, and refine the MUE to the setting.
- Add stakeholders from support departments, such as finance or quality, to the team.

Clarify current knowledge of the process.

Every MUE requires a starting point or practice standard and measures to evaluate performance. Whether the process is prescribing (e.g., adherence to established guidelines) or dispensing (e.g., accurate and timely preparation and delivery), the “current state” must be determined. This requires the development of process and outcome measures, data elements to collect, and sources for the data. The “current state” evaluation for a prescribing process might involve reviewing medical records and order sets, reaching a consensus on institutional guidelines for prescribing, or reviewing approval documentation (when a formal stewardship process is in place). The “current state” for a preparation and dispensing process can include a review of the existing policies and procedures, dispensing records, and real-time development of a process flow chart (i.e., what is observed in practice vs. what is expected). The AP began the process by sharing their existing policies,

procedures, guidelines, and the most relevant publications, ensuring that the most current evidence was included. Since several types of organizations were represented, there was much discussion about site-specific implications when designing guidelines. These site-specific considerations are particularly relevant when developing guidelines for system-wide implementation across several organizations or regions. For example, in our AP, some sites had access to rapid turnaround for anti-Xa activity levels, while others did not, which would impact clinical decision-making and process design. There was also much discussion about the scope of the guidelines; for example, would they include all reversal agents, and should it be assumed that a reversal agent is readily available? The AP also weighed in with their experiences, revealing several best practices and tips to consider when developing the MUE. See Appendix A and B for the MUE templates to review the two selected medication use questions. After outlining the guidelines and reaching a consensus, the AP mapped out the prescribing process, starting from when the patient presents until the order is placed. The same discussion occurred for the process of dispensing andexanet (i.e., from the time the order is placed until the drug is administered to the patient). Figure 2 is a diagram of the process map developed by the AP. During process mapping, it is important to identify specific outcomes desired at various points in the workflow (i.e., key process measures) and any potential delays and common places where the process can be unpredictable (i.e., opportunities for improvement). Once mapped, the process can be observed or data collected via the electronic health record (EHR) to better understand where and to what extent variation occurs in actual practice. The AP's flowcharting process identified several key process elements and desired measurable outcomes (see Figure 2).



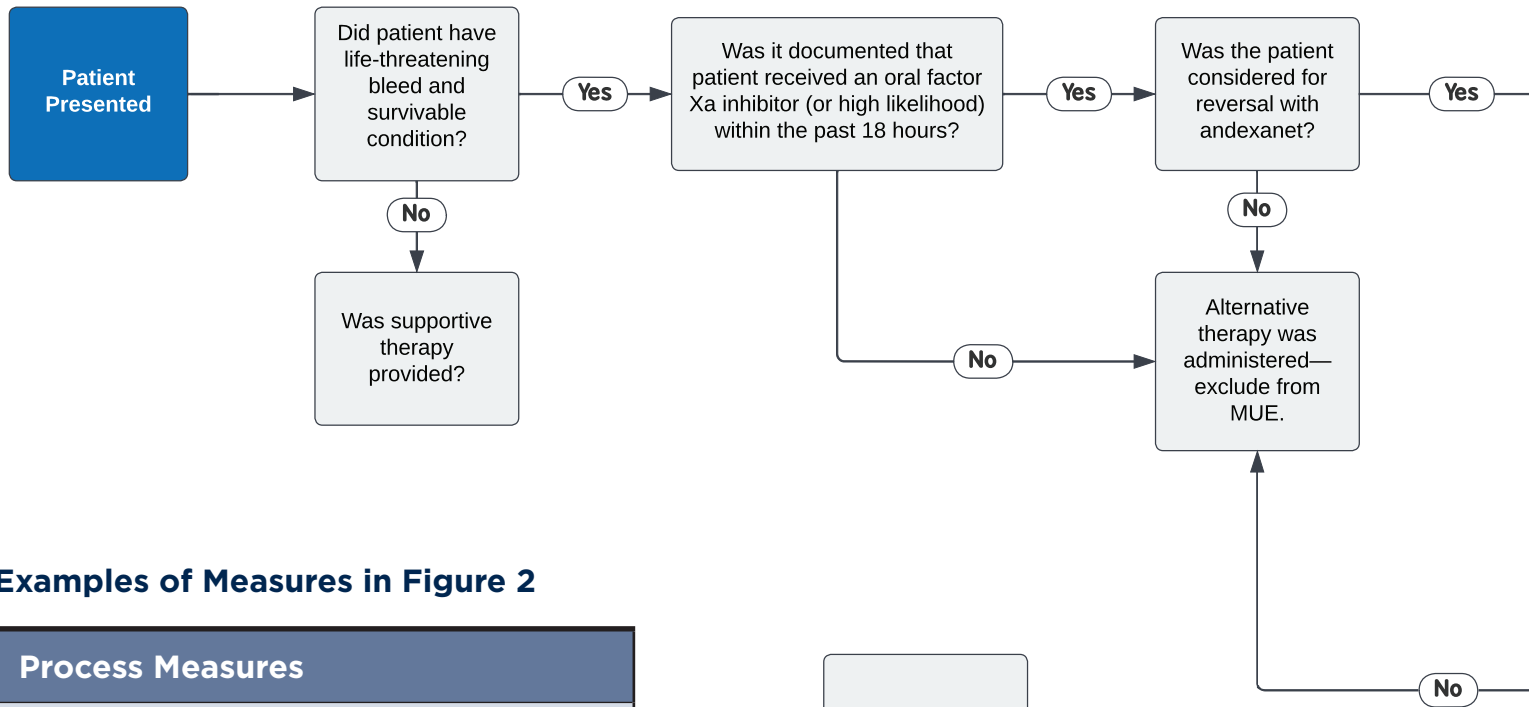
TIPS AND STRATEGIES: Clarify the Process

- When updating organizational guidelines, consider approved labeling, build upon current consensus guidelines, review new literature, and refine it to the setting.
- As a group, review the current processes and identify key process elements and desired measurable outcomes.
- Identify key process elements and desired, measurable outcomes, relevant and easy to obtain or collect.

Understand the causes of process variation.

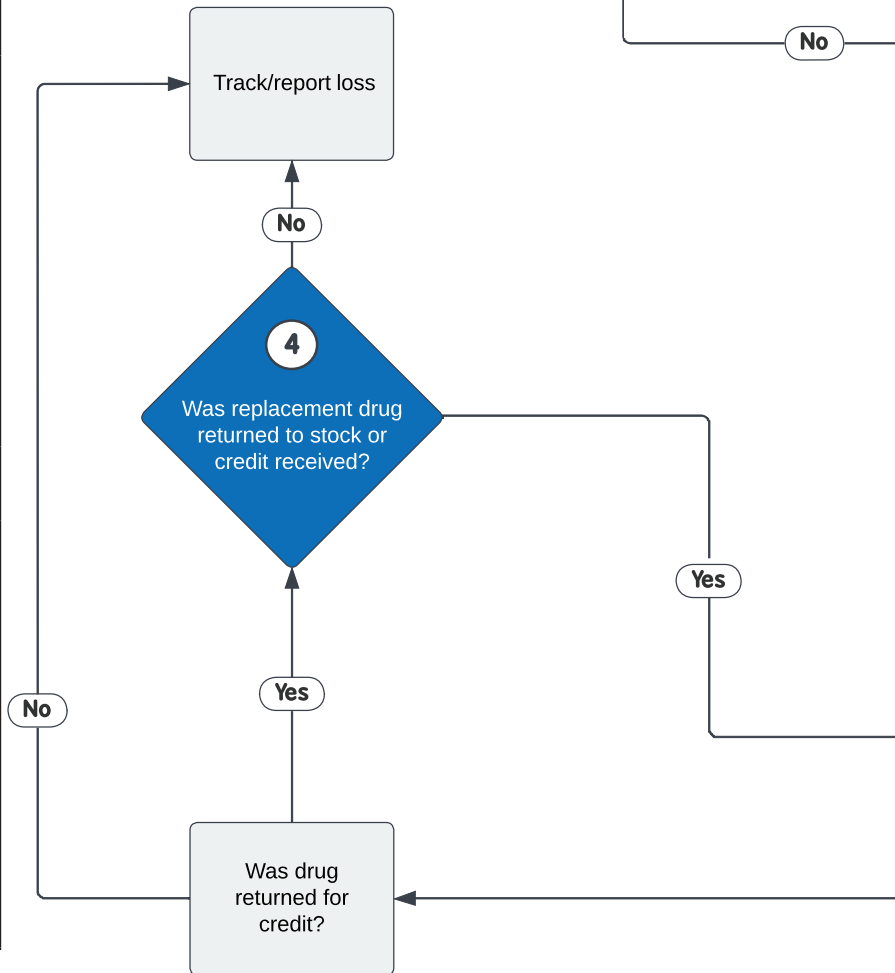
There are several types of performance measures: structure, process, outcome, and balancing measures.¹⁴ Quite often, MUEs are designed using process and outcome measures. Outcome measures are sometimes more difficult to report because some outcomes may only be measured after the patient is discharged, such as when a patient is discharged from a tertiary referral center and seen for follow-up outside the system. After identifying the key processes and outcomes, it is necessary to establish key measures and sources for the data. Data may come from observations, manually reviewing medical and dispensing records, and reports generated from the medical record. Appendix C lists additional examples of process and outcome measures, and Appendix D provides an example data collection framework.

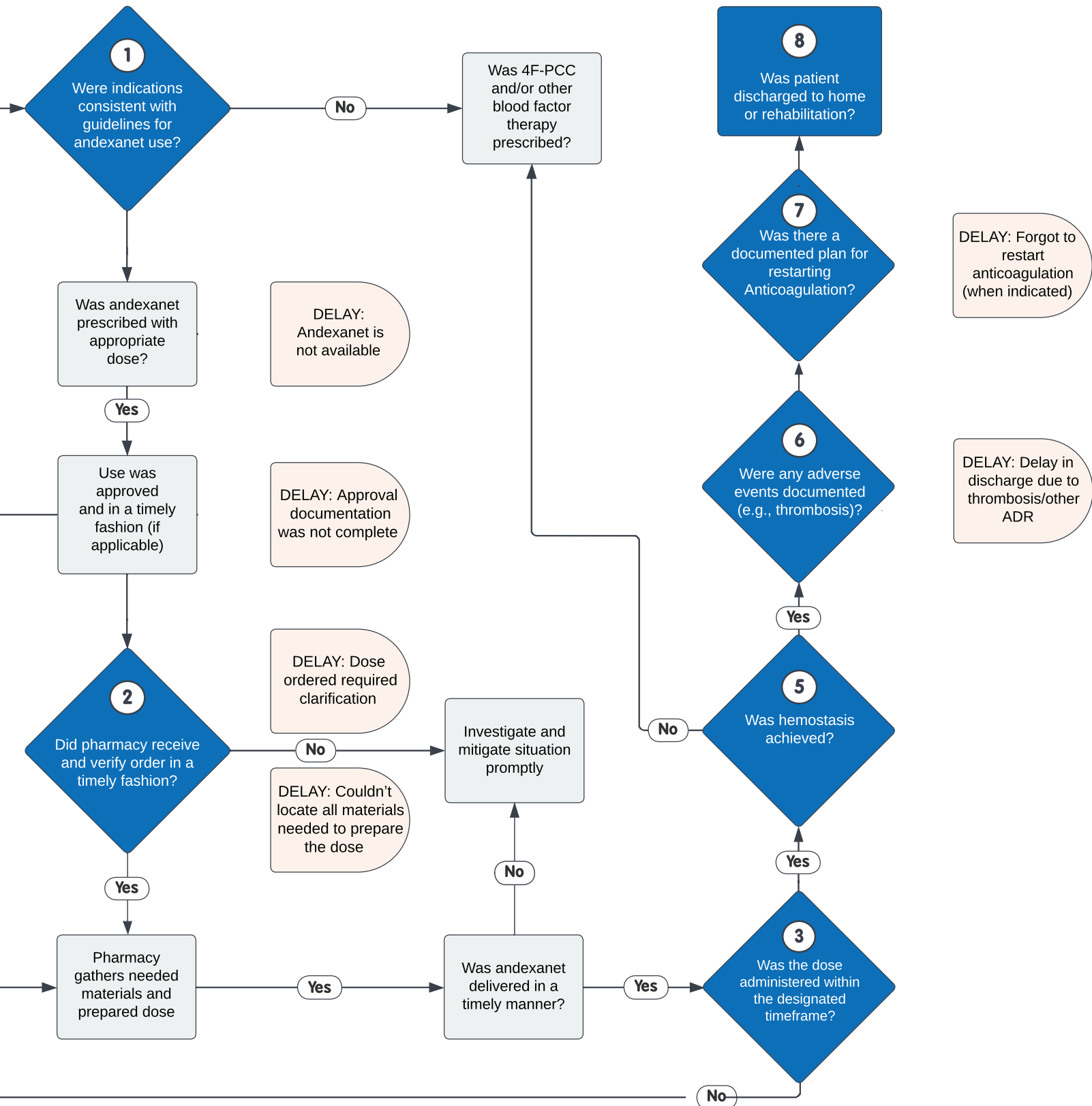
Figure 2. MUE Simulation Flowchart: Direct Oral Factor Xa Inhibitors



Examples of Measures in Figure 2

Process Measures	
①	Percent of orders where indication is consistent with approved guidelines
②	Percent of doses consistent with product labeling
③	Percent of patients administered the drug within one hour of order
④	Cost of drug products wasted (e.g., dose mixed but not administered)
Outcome Measures	
⑤	Percent of patients where hemostasis was achieved
⑥	Percent of patients with documented adverse event (e.g., thrombosis) during hospitalization
⑦	Percent of patients with documented plan for reinitiation of anticoagulation
⑧	Percent of patients discharged to home or rehab







**TIPS AND STRATEGIES:
Understand the Causes of
Variation**

- Try to have data collection as automated as possible (e.g., build fields/queries into the medical record or identify easily extractable measures) from existing databases.
- Develop a data collection form to facilitate data analysis; for example, a spreadsheet with standardized dropdowns or building an online survey with key data elements that can be downloaded to a spreadsheet.
- Only collect information relevant to the question(s) the MUE is trying to answer.

Select the process improvement.

Once the data are collected, they should be analyzed and presented to the team for review and discussion. Consider exceptions and outliers and whether the variance is reasonable (e.g., a unique exception or new study). In this case, there may need to be a change to the process design or guidelines to include the variance as an “acceptable” variation. Sometimes this analysis identifies unclear or unknown steps, sometimes called “clouds.” Examples of “clouds” are patients who cannot be located, missing test results, or a drug lost in transit. While the AP did not collect actual data during this simulation, they contributed experience from their organizations. Table 2 shows some examples of andexanet MUE process variances and possible tests of change to consider for process improvement.

It is best to be transparent in the data analysis and presentation, seek and incorporate input from the team, and ensure agreement in interpreting the results. Upon identifying variances, the team should discuss process improvement options. Ideas can occur through brainstorming and networking with other organization stakeholders or even colleagues. Questions to ask during this process include:

- Are there ways to reduce the variation (such as delays)?
- Are there ways to reduce waste (such as product waste or re-work)?
- Are there “clouds” in the process where it is unclear what has occurred?
- How have other organizations addressed these issues, or are there best practices?



**TIPS AND STRATEGIES:
Select the Process
Improvement**

- Create an environment where all ideas are valued, then prioritize them based on level of impact, resources required, and potential risk.
- Use caution when making changes based on outcome measures because MUEs often don’t have a robust enough study design to determine whether the outcome is statistically significant.
- Identify delays and “clouds” in the process as these are opportunities for improvement.

Table 2. Example MUE Variances and Tests of Change for Andexanet MUE

Measures	MUE Variance Examples	Example Tests of Change for Improvement
Process Measures		
1. Percent of orders where the indication is consistent with approved guidelines	Drug is prescribed when functional recovery is not possible	Implement required neurology consult
2. Percent of doses consistent with product labeling	Dosing is incorrect in some patients	Implement dosing protocol supported by order sets
3. Percent of patients administered the drug within one hour of order	Delay in administration related to time between order received and drug preparation	Create a kit with all supplies that is “ready to go”
4. Cost of drug products wasted (e.g., dose mixed but not administered)	By the time the drug gets to the patient, the order is discontinued	Unit-based pharmacist coordinates drug preparation
Outcome Measures		
5. Percent of patients who achieved hemostasis	A small number of patients did not recover despite drug administration and had not met the guidelines	Reinforce guidelines with education
6. Percent of patients with a documented adverse event (e.g., thrombosis) during hospitalization	One patient developed thrombosis after therapy was administered	Evaluate the process for restarting anticoagulation or alternative therapy
7. Percent of patients with a documented plan for reinitiation of anticoagulation	Anticoagulation was not restarted in some atrial fibrillation patients	Build a restart prompt into the EHR
8. Percent of patients discharged to home or rehab	Several patients with ICH died prior to discharge or transferred to other hospital	Require neurology/ neurosurgery consult to participate in the decision to prescribe reversal agent

Tests of Change: Plan, Do, Check, Act

The next phase of the process improvement is implementing the test(s) of change identified by the MUE team and evaluating the change, known as the Plan/Do/Check/Act (PDCA) cycle. Team members should work together to develop the specific solution and timeline for implementation and any education or information system changes that need to be made (Plan). It is ideal to have one person identified as the champion for the process improvement. Sometimes it is best to study the change in one area before moving it out to the organization (Do). Once the change is implemented, it should be measured and the results evaluated (Check). Successful changes should be scaled and reassessed to ensure that the gain has been sustained or to update the process or guideline (Act). The results of an MUE, as well as proposed or implemented changes and improvements from those changes, should be shared with relevant organization committees.

Conclusion

A multidisciplinary team applied the FOCUS-PDCA framework in a simulation to develop an MUE assessing the use of reversal agents to manage bleeding in patients on oral factor Xa inhibitors. By applying this framework and the ASHP guidelines, organizations can optimize medication use, reduce process variation, decrease waste, and enhance value.

Funding

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Appendix A: 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 [Andexanet]

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 (i.e., a decrease of ≥ 2 g/dL hemoglobin and/or administration of ≥ 2 units of RBCs)
- Determination of whether bleeding was critical (i.e., critical site bleed or life-threatening)^d
- Determination of whether this was a salvageable condition [for example, if intracerebral hemorrhage (ICH) consult stroke neurologist or neurosurgeon who will determine salvageability (e.g., consider cutoffs for GCS and ICH scores and ICH volume consistent with the ANNEXA-4 trial)]
- Collateral issues weighed (e.g., 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 (e.g., ≥ 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



PROCESS IMPROVEMENT

TIP: Convene a multidisciplinary team to discuss their thought process when deciding to treat, then identify where there is clear evidence or nationally-recognized guidelines, then apply those guidelines to the setting (e.g., what laboratory tests are available and their turnaround time, is there a process for approval, does the electronic health record (EHR) provide decision support, are providers with the required expertise available 24/7?)

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 (e.g., 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



PROCESS IMPROVEMENT

TIP: Consider building inclusion criteria into a pre-defined order set.

Applicable clinical tests and monitoring initiated

- Laboratory tests
 - CBC
 - Hepatic function
 - Renal function
 - PT, aPTT, Anti-FXa assays^f
- For critical site bleeding
 - Serial imaging tests (e.g., 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 (e.g., neurology/neurosurgery)
 - GCS is calculated, if applicable
 - ICH score is calculated, if applicable
- For GI bleeding
 - Gastroenterology consult is obtained



PROCESS IMPROVEMENT

TIP: Identify ways to capture monitoring and laboratory data via structured data fields within the EHR.

^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; ICH, intracranial hemorrhage; MUE, medication-use evaluation; MRI, magnetic resonance imaging; PT, prothrombin time; RBCs, red blood cells
^b This is an example set of MUE criteria. Each institution should establish guidelines and MUE criteria appropriate to the setting.
^c The MUE template assumes that andexanet alfa is available for administration.
^d For 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
^e 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.
^f Assays specific for apixaban and rivaroxaban quantitation are specialized and are not widely available. Assays that are calibrated for each agent to estimate plasma concentrations may not be available or the results may not be available to inform treatment decisions.

Appendix B: MUE Template: Dispensing Process

Medication Use Question #2: Has the pharmacy implemented processes to ensure safe and cost-effective use of andexanet?^{a,b,c}

MUE CRITERIA

FXa Inhibitor Reversal: Focus on andexanet alfa [Andexanet]

Order had all required elements

- Anticoagulant to be reversed was an oral Factor Xa-inhibitor
- Strength of last dose (or stated as unknown)
- Timing of the last dose or if unknown
- Andexanet dose (high or low) is correct

Key elements for consideration are documented in the electronic health record

- Indication (e.g., 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 (e.g., high thromboembolic risk)

Approval process was timely

- Required clinical information is documented in the electronic health record (EHR)/date, time
- Indication confirmed/documented in EHR/date, time
- Approval confirmed (if applicable)/date, time, and name of individual approving
- Order date/time
- Preparing pharmacist notified/time of notification



PROCESS IMPROVEMENT TIP:
Consider building a defined order set or, with clinical decision support guidelines, a checklist with fields within the EHR to document key information required for dosing and administration.

Pharmacy/Sterile Products was alerted “stat”

- The pharmacist verified the appropriate dose
- Dose was prepared and delivered by the pharmacist or pharmacy technician to the nurse
- Dose was dispensed/date, time



PROCESS IMPROVEMENT TIP:
Consider including pharmacy on stroke team notification, “stat” routing of the order, and/or prioritization within the order verification queue.

Prescribed dose was administered in a timely fashion

- After reconstitution by the pharmacy, andexanet alfa stored at room temperature was used within 8 hours, or 4 hours^d if prepared at the bedside
- Bolus dose administered, then, within 2 minutes following the bolus dose, continuous IV infusion at a rate of 30mg/minute was administered
- End time for infusion documented
- When the infusion is complete, line flushed using 50mL bag of 0.9% sodium chloride to ensure that the entire dose was administered
- Any arterial and venous thromboembolic events, ischemic events, and cardiac arrests that occurred after the start of andexanet alfa were noted in the EHR



PROCESS IMPROVEMENT TIP:
Consider having a kit that includes supplies for preparation readily available.



PROCESS IMPROVEMENT TIP:
Using the same tubing from the bolus and connecting it to the infusion helps to minimize waste.

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

b This is an example set of MUE criteria; each institution should establish guidelines and MUE criteria (e.g., parameters for timeliness) appropriate to the setting.

c The MUE template assumes that andexanet alfa is available for administration

d USP 797 Pharmaceutical compounding - sterile preparations, updated guidance, official November 1, 2023.

Appendix C: Example Measures for Andexanet Alfa DOAC Reversal Agent MUE

Prescribing Process Measures

- Indication for reversal is consistent with guidelines
- Document indications for reversal agent (e.g., ICH, non-ICH-related bleeding, pre-operative reversal)
- PCC, other factors or treatment given at an outside hospital
- Patient received 3-factor, 4-factor, activated factor 7, or aPCC within previous 48 hours of symptom onset
- Stroke neurologist consult documented
- Documented relevant comorbidities (e.g., diabetes, hypertension, liver disease, renal insufficiency, prior major bleeding event)
- Pre-andexanet alfa hemoglobin and hematocrit obtained within 24 hours of andexanet alfa administration
- Radiology (CT) scan image obtained and interpreted
- For ICH patients: Imaging described ICH volume before and within 24 hours after administration of andexanet alfa
- For ICH patients: Glasgow Coma Scale or ICH score at the time of symptom onset and before receiving any sedative medications
- Pre-andexanet alfa anti-Xa level order placement, collection time, level result^a

Medication-Use Process Measures

- Time of last administration of an oral factor Xa inhibitor documented within 18 hours
- Andexanet dose consistent with guidelines
 - Strength of the last dose
 - Timing of the last dose
- If required, approval was obtained before dispensing
- Weight-based dosing is appropriate
- Time from order placed to drug delivery/drug administered is within the designated timeframe
- Drug is not wasted (e.g., prepared but not administered)
- Presence and time/date of adverse thrombotic or major bleeding events within 14 days of andexanet alfa administration or before hospital discharge (whichever occurs sooner)
- For patients requiring andexanet alfa pre-operatively:
 - Number of units of pRBC used within 24 hours following andexanet alfa administration
 - Intraoperative estimated blood loss
 - Occurrence of thromboembolic events
- If indicated, time of anticoagulation resumption

Outcome Measures

- Patients with ICH or non-ICH bleeding who achieved good hemostasis six hours after andexanet alfa administration (e.g., whether hemostasis was achieved within 48 hours following reversal as defined as not having hemodynamic instability, decrease in hemoglobin of 2 g/dL or bleeding requiring blood transfusion)^b
- Absence of progression of ICH
- Blood transfusion, 3-factor, 4-factor, activated factor 7, or aPCC required
- Length of hospital stay
- Length of ICU stay
- If indicated, thrombosis risk assessment and time of anticoagulation resumption
- Medication review and reconciliation
- Time of the thromboembolic or major bleeding event within 30 days or before hospital discharge (whichever occurs sooner)
- Return to functional status/ADLs
- 90-day modified Rankin Score
- Requires surgery
- Mortality within 30 days of reversal
- Andexanet alfa billing and hospital coding

^a Assays specific for apixaban and rivaroxaban quantitation are specialized and are not widely available. Assays that are calibrated for each agent to estimate plasma concentrations may not be available or the results may not be available to inform treatment decisions.

^b Refer to validated scales for definitions for the different bleeds.

Appendix D: Example Data Collection Framework for DOAC Reversal Agent MUE

Data Element	Response Format (Spreadsheet)
Patient Initials or internal control number	Text or Numeric
Patient Medical Record Number	Numeric
Date of birth	Date <i>(Use birth date vs. age.)</i>
Height	Numeric <i>(Use measure to allow calculation of BMI, use most recent value.)</i>
Weight	Numeric <i>(Use measure to allow calculation of BMI, use most recent value.)</i>
Encounter Date and Time	Date and Time Format <i>(Use format for calculation of length of stay.)</i>
Discharge Date and Time	Date and Time Format <i>(Use format for calculation of length of stay.)</i>
Final DRG Code assigned	Numeric
Race/Ethnicity	Drop Down: Native American/Asian/African/American/Hispanic/Latino/Pacific islander/White/More than one/Not reported
CT Scan ordered and read	Drop Down: Yes/No and Date and Time format
For ICH, GCS or ICH score documented	Drop Down: Yes/No and Date and Time format
Time of pre-andexanet alfa anti-Xa level order placement	Time of pre-andexanet alfa anti-Xa level order placement
Anticoagulant	Drop Down: Apixaban/Edoxaban/Rivaroxaban
Anticoagulant dose	Drop Down: 2.5 mg/5 mg/10 mg/15 mg/20 mg/30 mg/60 mg/Other
Regimen	Drop Down: Once daily/ Twice daily/Other
Last Dose of Anticoagulant	Date and Time Format <i>(Use format for calculation of treatment window.)</i>
Coagulation Laboratory Testing	Drop Down: aPTT/PT/PT-INR/Anti-Xa level (heparin)/Anti-Xa level (LMWH)/Anti-Xa Level (apixaban calibrated)/Anti-Xa Level (edoxaban calibrated)/Anti-Xa Level (rivaroxaban calibrated)
Coagulation Testing Date and Time	Date and Time Format
Laboratory Result:	Numeric, Units
Hematology Laboratory Testing	Numeric, Units
1 st Reversal agent	Drop Down: Andexanet/3-factor/4-factor/activated factor 7/aPCC
2 nd Reversal agent	Drop Down: Andexanet/3-factor/4-factor/activated factor 7/aPCC
Indication	Drop Down: Per organization's approved guidelines
Bleeding Site	Drop down: Gastrointestinal/Intra-articular/intracranial/Pericardial/Pulmonary hemorrhage Intraspinal/ Intramuscular Retroperitoneal/Other
Reversal Physician Order Date and Time	Date and Time Format <i>(Use this format for calculation of door-to-diagnosis time.)</i>
Reversal Order Pharmacy Verification Date and Time	Date and Time Format <i>(Use format for calculation of Pharmacy order verification time.)</i>
Reversal agent Pharmacy Prep Date and Time	Date and Time Format <i>(Use format for calculation of Pharmacy prep time.)</i>
Reversal agent Pharmacist Check Date and Time	Date and Time Format <i>(Use format for calculation of Pharmacy prep time.)</i>
Reversal agent Pharmacy Delivery Date and Time	Date and Time Format <i>(Use this format for calculation of Pharmacy prep time.)</i>
Reversal Agent Administration Date and Time	Date and Time Format <i>(Use this format for calculation of door to treatment time.)</i>
Reversal agent dose	Dropdown: Andexanet: 400 mg bolus/480 mg infusion/800 mg/960 mg infusion/4 factor PCC dosing per hospital policy
Blood product Physician Order	Date and Time Format <i>(Use this format for calculation of door-to-diagnosis time.)</i>
Blood product	Drop down: RBC/FFP/Platelets <i>(Use this format for calculation of door-to-diagnosis time.)</i>
Blood product Physician Administration	Date and Time Format <i>(Use this format for calculation of door-to-diagnosis time.)</i>
Patient Outcome	Drop down: Deceased/Survive to discharge/thromboembolic event within 14 days or before discharge, whichever comes first
Adverse Event	Drop down: Thrombosis or re-occurrence of bleeding within 30 days of andexanet alfa administration or prior to hospital discharge (whichever occurs sooner)

Appendix E: Selected References and Resources for DOAC Reversal Agent MUE

Guidelines

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