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Systematic Approach to Academic Detailing & Formulary Decision-making for High-cost, High-risk Medications

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Our Presenters

Systematic Approach to Academic Detailing & Formulary Decision-making for High-cost, High-risk Medications

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Speaker Disclosures

- The presenters have no real or perceived conflicts of interest related to this presentation.
- Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

Learning Objectives

At the end of this session, participants should be able to:

- Define a system formulary management process
- Identify key representatives to support a system-based approach to formulary management
- Develop a process to empower P&T representatives to engage in academic detailing and peer-to-peer engagement to address controversial formulary decisions

Overview

- Scripps Health and System P&T overview
- Discuss Scripps system formulary management process
- Review unique challenges to the formulary review workflow
- Review two case examples requiring a modified approach
  - Angiotensin II
  - Andexanet alfa
- Discuss future opportunities

Scripps Health

System Overview

- Non-profit, integrated healthcare system in San Diego

- 4 hospital health-system with 5 campus locations
  - Scripps Memorial Encinitas
  - Scripps Green
  - Scripps Memorial La Jolla
  - Scripps Mercy
    - ✓ San Diego Campus
    - ✓ Chula Vista Campus

- Scripps Health System
  - Scripps Clinic and Scripps Coastal Medical Center outpatient medical centers/clinics

- Scripps MD Anderson Cancer Center

Scripps Health

Pharmacy and Therapeutics Council

- Pharmacy and Therapeutic Council (System P&T) re-established in 2016

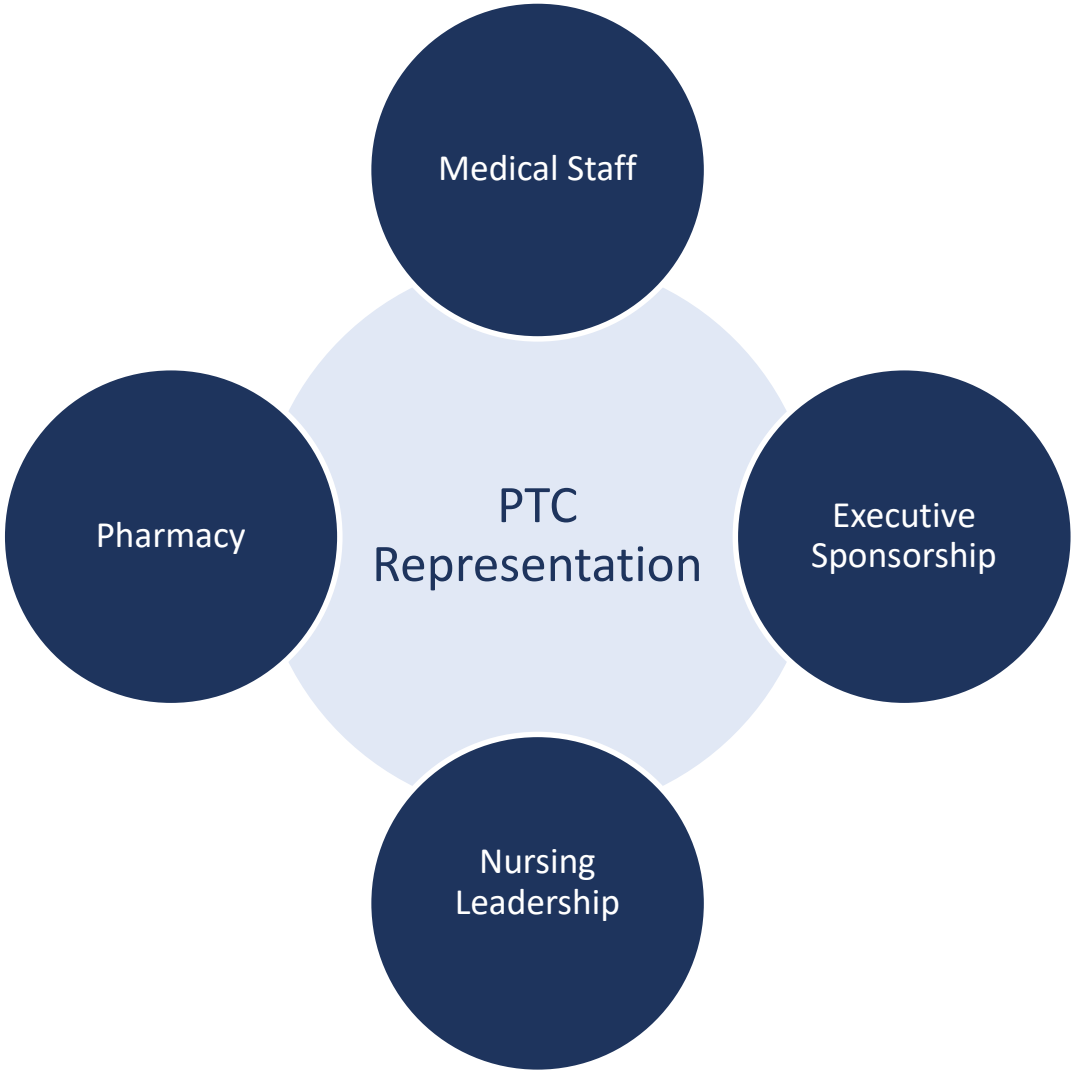
- Goals
  - Develop a system-level governance structure for formulary stewardship and financial impact monitoring

  - Ensure transparency in all processes and decisions
    - ✓ Engage key physician stakeholder groups early and throughout any review processes
    - ✓ Utilize various communication tools to inform providers of P&T decisions and upcoming implementation items

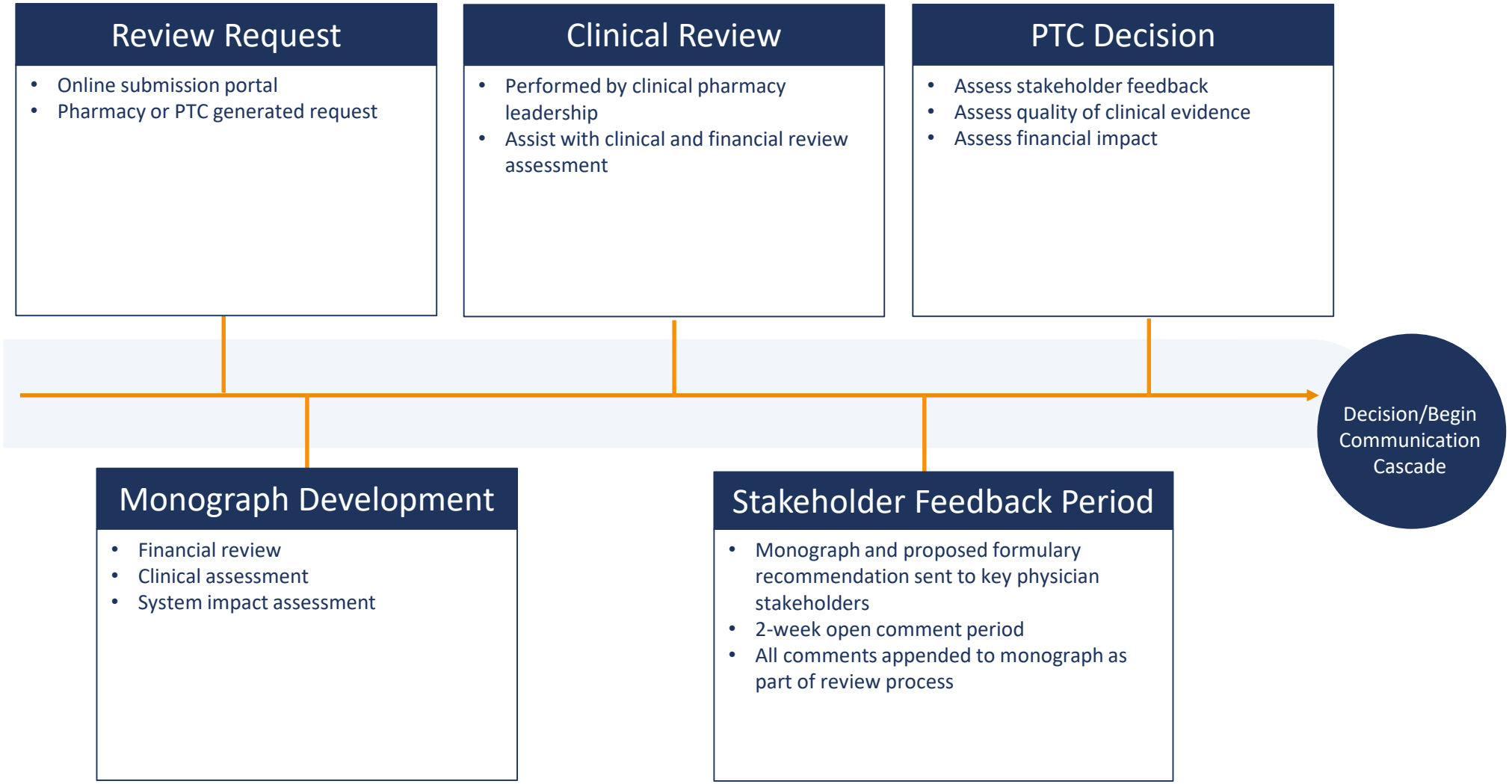
  - Establish separate system and site P&T responsibilities to improve efficiency and eliminate redundancies

Pharmacy and Therapeutics Council

Membership



PTC Formulary Review Process



PTC Formulary Review Process

- Often a uni-directional workflow until the final decision is reached
  - Feedback collected and presented to PTC
  - Decision is then fed back to stakeholders and the general medical staff
- PTC membership typically prefers to move things forward with full consensus as opposed to up-or-down voting
- Traditional feedback model for stakeholders that disagree with a PTC decision is a formal appeal process

Pharmacy & Therapeutics Council

Unique Formulary Review Challenges

- When evidence and professional opinion are in conflict
- Challenge further complicated when the potential cost impact is significant
- Two recent reviews presented unique challenges that required adaptations to the usual workflow

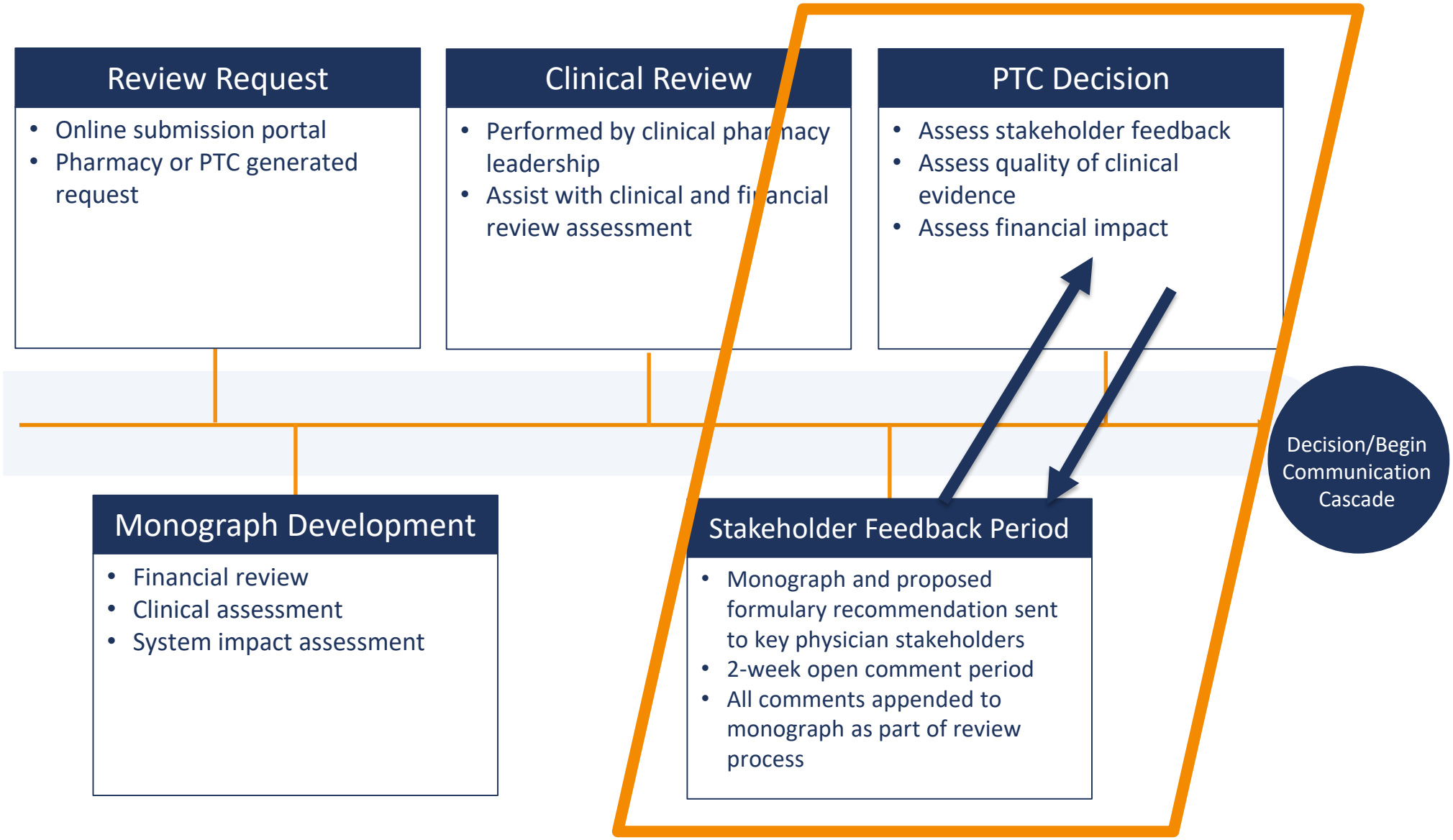
Formulary Review	Evidence Assessment	Stakeholder Concerns	PTC Decision
Angiotensin II	Unclear benefit compared to vasopressors on formulary	Unique mechanism of action Should have this available as a last resort regardless of study limitations due to high mortality associated with sepsis	Non-formulary Allow utilization pursuant to specific patient criteria Track utilization and reassess after one year
Andexanet alfa	Unclear benefit in patient population of interest as compared to usual care with 4-factor PCC	First antidote for direct oral Xa inhibitors Concern that there may be a medical-legal issue if this agent is not available for use	Non-formulary and not stocked No use permitted even on a case-specific basis

Angiotensin II

Formulary Review

- Naturally occurring peptide hormone indicated for the management of distributive shock
- Marketed as an effective non-catecholamine alternative vasoactive agent to raise blood pressure in patients with shock
- Major critiques identified by the review team
  - No clear benefit over available alternatives with regard to patient outcomes
  - Available safety data inconclusive
  - Cost prohibitive as compared to formulary alternatives
- Estimated to cost 4x more per day as compared to vasopressin
- Controversy
  - Limited options available for shock
  - Septic shock has a high mortality rate and physicians should have all options available to them
  - Concern that lack of availability may present medical-legal issues

PTC Formulary Review Process Revisited



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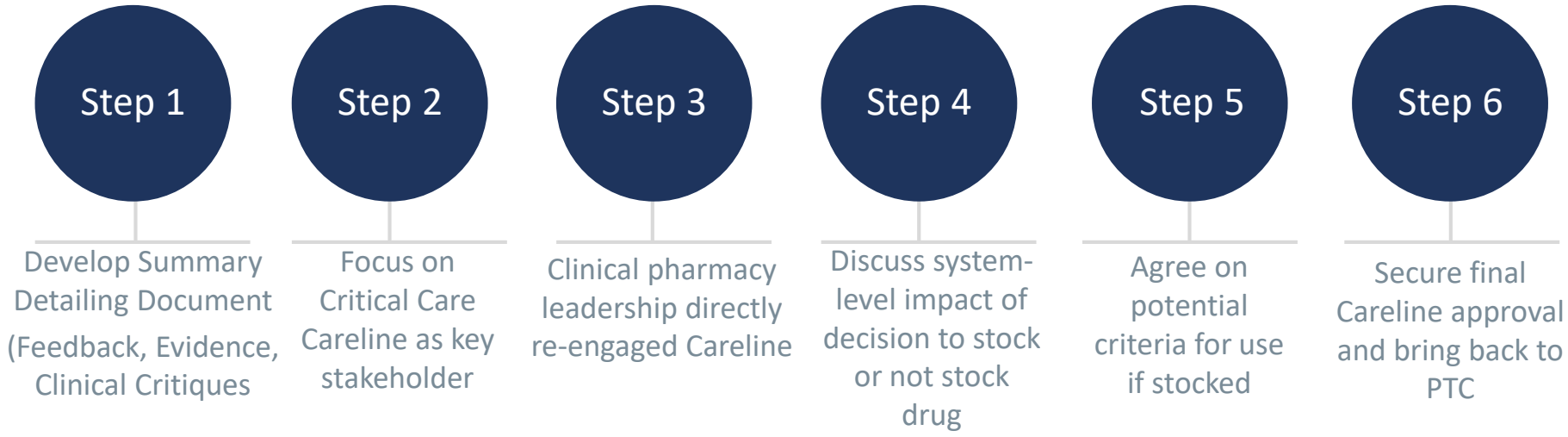


Focused Detailing Document

- Summarize key findings from the clinical review process including critique of the available literature and applicability of evidence to the local patient population
- Revisit potential financial impact to the system
- Summarize feedback from both stakeholders and members of PTC received to date

Angiotensin II

Formulary Decision Revisited

- Critical Care Careline proposal
  - Allow limited use pursuant to strict criteria for use
  - Agree to formal review after 6-12 months
    - ✓ Compliance with use criteria
    - ✓ Gauge therapeutic effectiveness and possible indirect cost savings (CRRT, ECMO)
    - ✓ Reassess available literature
    - ✓ Revisit formulary status and consider elimination of all use if not found to be effective
- PTC reviewed Careline feedback and proposal
  - Angiotensin II approved for limited non-formulary use pursuant to established criteria and planned formal review in 6-12 months
  - Clinical pharmacy leadership tasked with developing data collection process
- Coordinated with Epic team to develop a new order panel with use criteria clearly outlined and a custom report to track utilization on a routine basis
- Critical Care pharmacists tasked with completing a questionnaire after each approval (if possible, document CRRT/ECMO avoidance)

Angiotensin II Criteria for Non-Formulary Use

ANGIOTENSIN II
CRITERIA FOR USE

CRITERIA for USE:

Angiotensin II is made available on a provisional basis, as a non-formulary medication. Patients having any one of the exclusion criteria shall not receive this medication. Consideration for use is restricted only for patients meeting ALL inclusion criteria who do not have extensive co-morbidities that predict low likelihood of survival.

- Angiotensin II is restricted to Medical Intensivist and Trauma Intensivist use only. (No Residents/fellows without attending)
- Angiotensin II may only be prescribed by using an order set.
- Angiotensin II will be discontinued when patients do not respond to therapy, defined as after having received angiotensin II at maximal doses (i.e. 40 - 80 ng/kg/min) for 3 consecutive hours and have not reached goal MAP ≥ 65 mmHg or a rise of ≥ 10 mmHg from baseline

Angiotensin II Criteria for Non-Formulary Use

EXCLUSION CRITERIA:

- Acute coronary syndromes
- Liver failure (MELD score ≥ 30)
- Mesenteric ischemia or history of
- Active bleeding
- History, presence, or suspicion of abdominal aortic aneurysm
- ANC < 1,000
- Hypotension not associated with septic shock
- Age < 18 years
- Requiring more than 500mg per day of hydrocortisone or equivalent
- Expected life span < 12 hours
- Allergy to mannitol
- Pregnant
- Exposure to ARB within last 48 hours*

* ***predictor of poor response***

INCLUSION CRITERIA (patient meets ALL 3 items below):

1. Medicare definition for sepsis, for patients in septic shock. (see attached)
2. Appropriate fluid resuscitation (such as 30 mL/kg) of fluid after meeting sepsis criteria
3. Currently receiving 3 of the 4 medications below (at indicated rates) for at least 1 hour and still have MAP < 65 mm Hg:

    a. Norepinephrine ≥ 35 mcg/min **PLUS**
    b. Vasopressin ≥ 0.03 units/min
    AND 1 of the following:
    c. Epinephrine ≥ 10 mcg/min **OR**
    d. Phenylephrine ≥ 200 mcg/min.

Angiotensin II Non-formulary Use – Data Collection Form

1. Were all criteria for use met at the time of order? ☐ Yes ☐ No
2. Were any exclusion criteria identified at the time of order? ☐ Yes ☐ No (If yes, please list below)
3. Did the patient respond to therapy (attained MAP ≥ 65 mmHg or an increase of ≥ 10 mmHg)? ☐ Yes ☐ No
4. If the patient did NOT respond to therapy, was the drug promptly discontinued? ☐ Yes ☐ No
5. Was the maximum infusion rate as written in the default order exceeded? (80 ng/kg/min for first 3 hours, 40 ng/kg/min thereafter) ☐ Yes ☐ No

For sites where ECMO is performed or patients are routinely transferred to receive ECMO please discuss the following with the ordering provider if possible:

1. In their assessment at the time angiotensin II was ordered, was the patient a potential candidate for ECMO? ☐ Yes ☐ No
2. Did a positive patient response to angiotensin II specifically, prevent or delay the need for ECMO? ☐ Yes ☐ No

Angiotensin II

Formulary Decision Revisited

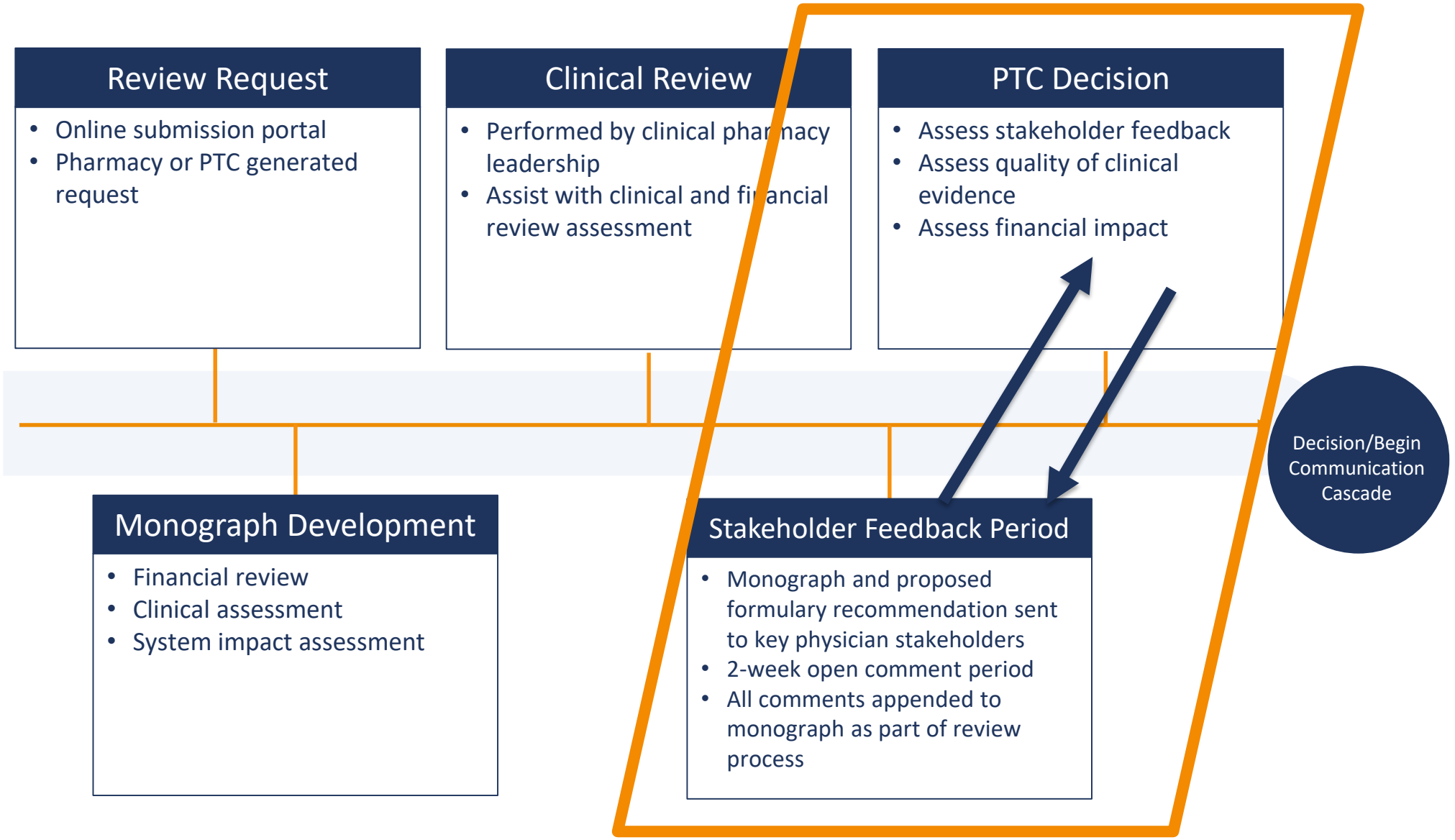
- Current State
  - Angiotensin II approved for use 25 times since PTC decision
  - Data for all patients reviewed and summarized
- Planned reassessment
  - Presentation summarizing all utilization, outcomes, and cost impact finalized
  - Critical Care Careline requested information on community utilization of angiotensin II
  - Clinical pharmacy leadership presented findings to the Critical Care Careline
- Careline determination pending (delayed following pandemic response)
- PTC to defer to Careline initially, with plans to make an independent decision if they do not reach consensus

Andexanet alfa

Formulary Review

- Exerts procoagulant effect by binding and sequestering the factor Xa (FXa) inhibitors. Andexanet alfa is also able to bind and inhibit the activity of tissue factor pathway inhibitor (TFPI) which can increase thrombin generation
- FDA approved for patients with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
- Many guidelines have suggested that once available, specific/targeted reversal agents should be used
- Annual estimated cost of $600,000 to $1.4M increase when used in lieu of PCC
- Initial strong stakeholder desire for widespread utilization of agent

PTC Formulary Review Process Revisited



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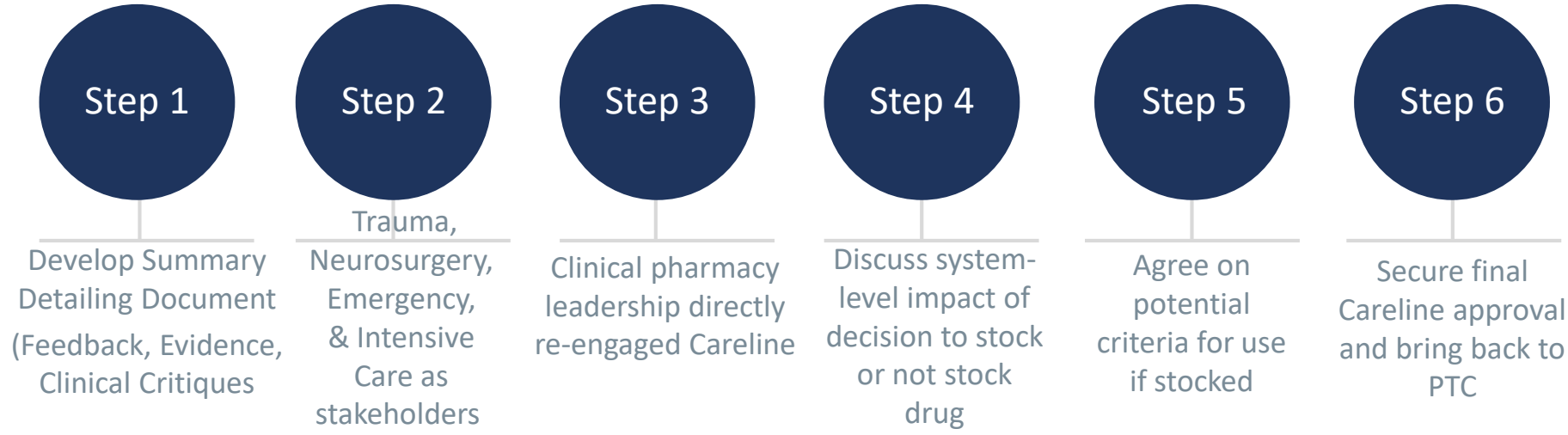

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- Summarize feedback from both stakeholders and members of PTC received to date

Andexanet alfa

Formulary Review

- Began literature and formulary review prior to release of agent
- Early engagement with legal team to determine if lack of availability would present a medical-legal issue
- Extensive review of best practices locally and across the nation
- Prepared detailed summary document to engage stakeholders

Andexanet alfa

Formulary Review Summary Document

- Major critiques identified by the review team
  - ANNEXAA-4 Study:
    - ✓ Lack of comparator arm
    - ✓ Anti-factor Xa level as a surrogate endpoint
    - ✓ Change in dosing scheme
  - Assessment of Andexanet vs. Standard of Care (PCC)
    - ✓ Unknown if andexanet is more effective or safer than usual practice or non-pharmacologic intervention
    - ✓ Not feasible to run rapid anti-Xa levels to exclude patients who demonstrate no anti-factor Xa drug activity
    - ✓ High dose regimen would be employed in many cases – may present increased thrombotic risk
    - ✓ Data does not support use immediately prior to/during emergent surgery
  - FDA has mandated that the manufacturer conduct a new clinical trial comparing Andexxa against “usual care,” which is likely to include use of PCC

Andexanet alfa

"BLUF" Document

Dear Stakeholders:

Andexxa® (andexanet alfa) is a new agent designed to reverse the anticoagulant effect of rivaroxaban or apixaban.

PTC's preliminary recommendation is to designate Andexxa® as Non-Formulary following a thorough review of the evidence and potential cost impact.

We are seeking your input. We encourage you to review the attached PTC monograph and full critique of the published ANNEXA-4 study.

Please submit your feedback to PTC by May 14th.

- Summary of ANNEXA-4 Study Results
  - 82% of patients reported to have excellent or good hemostasis at 12 hours
  - Hemostasis did not correlate with anti-Xa levels
  - Mortality rate of 14% (similar to literature on PCC) and thrombotic event rate of 10% observed (higher than reported with PCC)
- Major study critiques
  - No comparator arm: hemostasis results are hypothesis generating. **It is unknown if Andexxa performs better than placebo or PCC.**
  - Patients requiring emergent surgery were excluded. More severe ICH patients were excluded (hematoma volume > 60 cc or GCS < 7). For ICH bleeds, the mean GCS was 14, and hematoma volumes were <10 mL for 60% of patients.
  - Efficacy data censored for 33% of patients that received Andexxa following retroactive review of baseline anti-FXa levels
- FDA has mandated that the manufacturer conduct a new clinical trial comparing Andexxa against "usual care," which is likely to include use of PCC
- Estimated annual cost increase of $600,000 - $1.4M for Scripps when used in lieu of PCC

Andexanet alfa

Formulary Recommendation

- Pharmacy Service recommends non-formulary status for andexanet alfa
- PCC data is of similar quality with comparable outcomes however more representative of real-world clinical practice
- PCC is considerably more cost-effective
- Active comparator trial and surgical trial may yield more compelling results
- Non-formulary and not stocked; No use permitted even on a case-specific basis
- PTC members and stakeholders were engaged to provide academic detailing to colleagues
  - Pharmacy clinical leadership produced a standardized slide presentation summarizing key points and rationale for recommendation
- A formulary decision notification letter was sent to stakeholders to make them aware reasons behind the decision and the Carelines that endorsed it
- Official formulary decision – June 2019

Andexanet alfa

Current State

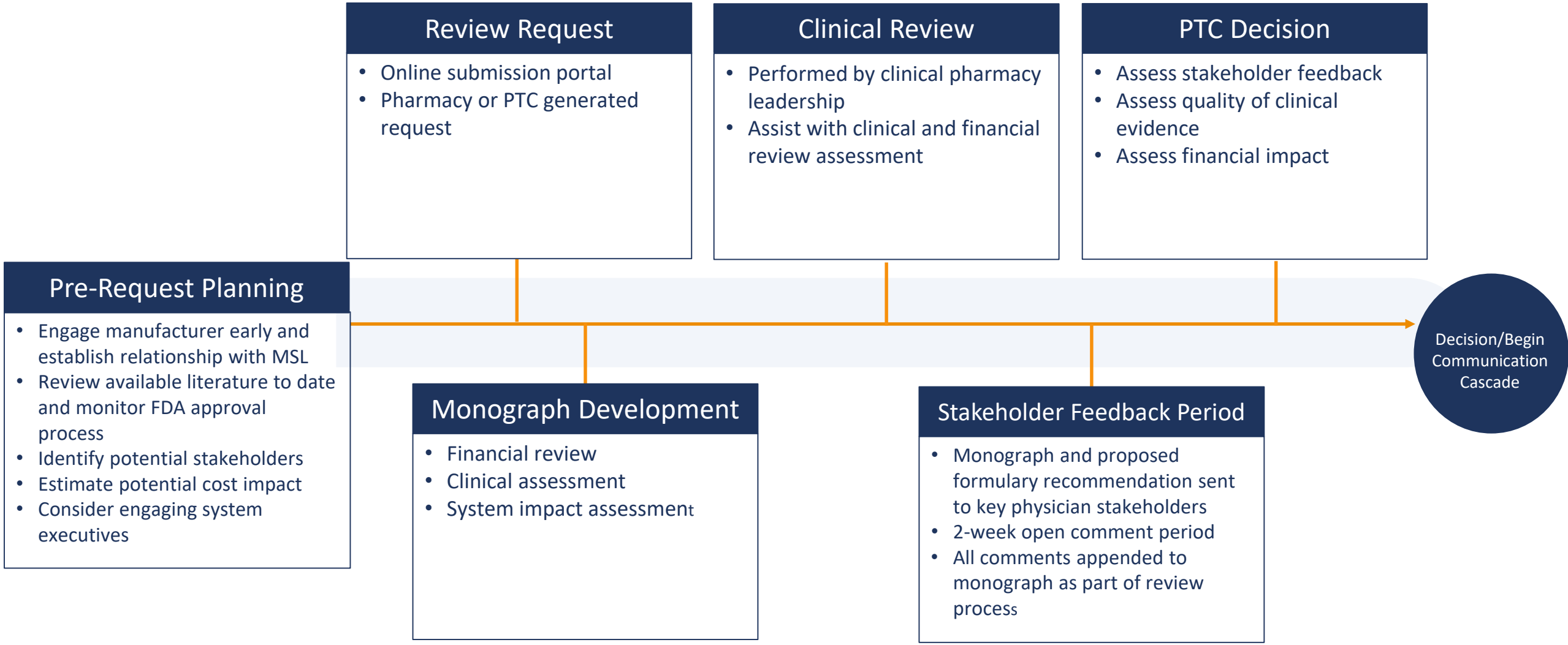
- There have been NO utilizations of andexanet alfa in the entire Scripps system
- Requests to pharmacy for use of andexanet alfa have not been frequent
- The early and frequent discussions with stakeholders to robustly review the data in open forums was very successful
- Engaging peers to in the academic detailing process was an additional successful strategy

Looking to the Future

HTX-011

- HTX-011 is an investigational drug not yet FDA approved
  - Extended release dual-acting local anesthetic
  - Designed to slowly release a mixture of bupivacaine and meloxicam following topical application at the site of the surgical incision
  - Purported to reduce post-operative pain and reduce the need for opioid analgesics in studies to date
- Ongoing marketing occurring in the San Diego region
- Anticipate a high degree of interest from surgery stakeholders within the system
- Recognize importance for coordinated effort on inpatient and ambulatory formulary

PTC Formulary Review Process – Modified Workflow



Looking to the Future

HTX-011

- Clinical pharmacy leadership evaluating literature to date
- Forecasting affected surgical types to anticipate potential volume of utilization
- Engaging manufacturer to get early cost estimates
- Next steps
  - Preview findings to PTC
  - Develop workgroup to engage identified stakeholder groups early to review evidence and pharamacoeconomic impact in a collaborative fashion
    - ✓ PTC Chair
    - ✓ PTC Surgical Representative
    - ✓ Pharmacy Leadership
    - ✓ Medical Foundation Leadership
  - Consider early engagement of executive leadership
  - Begin developing peer-to-peer academic detailing materials

Conclusion

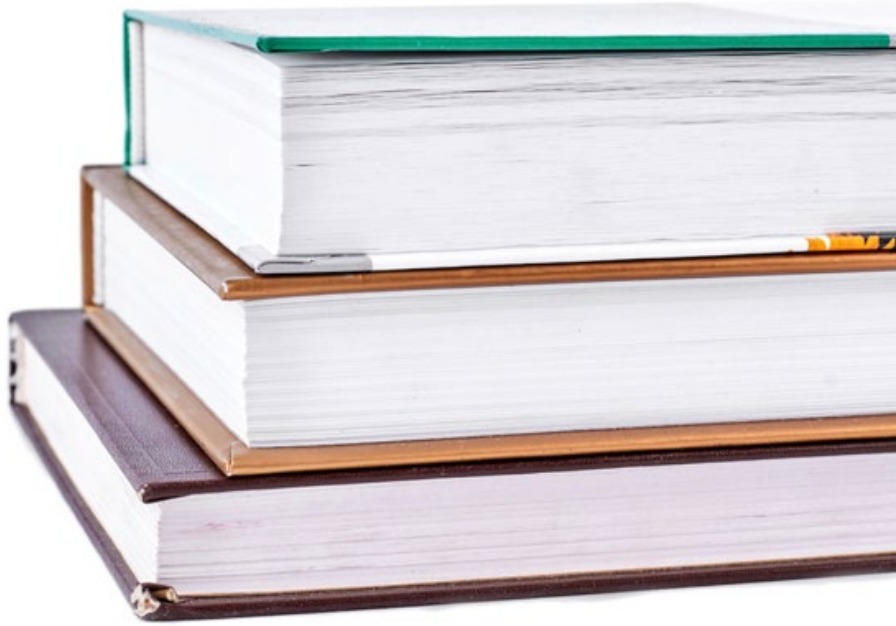
One Size Does Not Fit All!

- When it comes to high-risk, high-cost medications there is not always one approach that works best
- Understanding the needs of your stakeholders is key to a successful management process
- Early and frequent engagement is important
- Data review and real-world interventions will prove to be valuable tools in ongoing medication utilization
- Work collaboratively and allow physicians on your P&T committee to lead
  - Peer-to-peer academic detailing using standardized documents/presentations
  - Diverse representation of medical staff on the P&T committee is important

Assessment Question 1

Which of the following are elements of a system formulary management process?

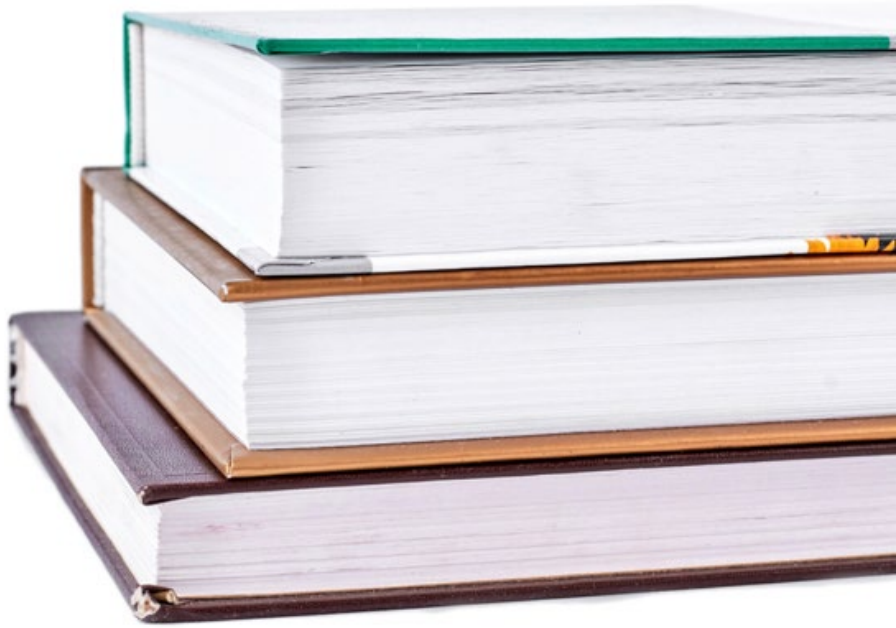
a. Conduct clinical reviews for new formulary requests
b. Engage pertinent stakeholders as part of decision making
c. Assess financial impact of formulary decisions
d. All of the above



Assessment Question 2

Which of the following would not be considered a typical stakeholder in supporting a system-based approach to formulary management?

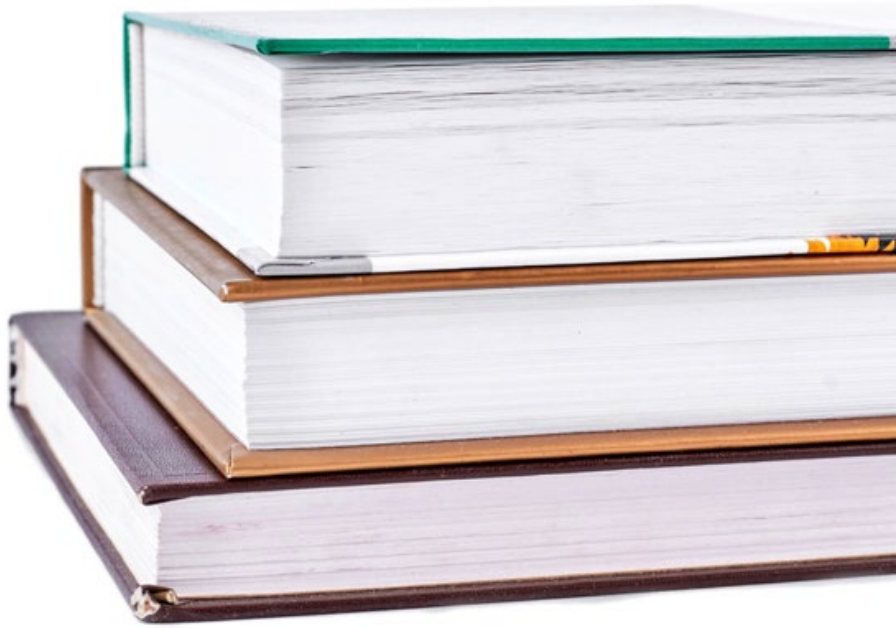
a. Intensivist
b. Nurse
c. Social Worker
d. Trauma Surgeon



Assessment Question 3

Which of the following is not a recommended strategy to address controversial formulary decisions?

a. Physician-led peer-to-peer academic detailing
b. Deny formulary status for expensive agents strictly due to cost
c. Critically evaluate the clinical and economic impact in a transparent and collaborative manner
d. Engage your health-system's legal department to address medical-legal questions



References

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Andexxa (Package insert).

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019 Apr 4;380(14):1326-1335

Reference note: The core content of this presentation reflects the internal workflow and thought processes of Scripps Health.

Thank you...

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