An Overview of One Formulary Making Decision Process

Annual AMCP Western Regional Conference
Napa, CA

June 28, 2015

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Disclosure Statement & Speaker's Non-Commercialism Agreement

- Rodney J. Gedey
- Presenter has no conflict of interest to disclose.
- This presentation was not funded.

The Learning Objectives

1. State the responsibilities of a P&T committee
2. Explain reasons to utilize prior authorization
3. Describe a formulary
4. List the main factors of a drug that are used to evaluate it for formulary placement
5. Discuss the difference between a confidence interval and a p-value

1. Which of the following products is least likely to be reviewed by a Pharmacy and Therapeutics committee?

A. A new FDA approved selective serotonin reuptake inhibitor
B. A new FDA approved IV antibiotic
C. A new FDA approved insulin infusion pump
D. A new FDA approved metal-on-metal implant for hip replacement

2. Which one of these is not a reason to utilize prior authorization?

A. Provide a barrier to patient care
B. Address the need for additional clinical patient information
C. Promote appropriate drug use and to prevent misuse
D. Administer step therapy

3. The definition of a formulary is a continually updated:

A. List of forms that members of a health plan use
B. List of medications and related information
C. List of inpatient procedures
D. List of current inpatient medication order sets

4. The _____ is responsible for managing the formulary system

A. American Pharmaceutical Association
B. Commission on the Accreditation of Hospitals
C. American Society of Health-System Pharmacists
D. P&T committee

5. The main advantage of a confidence interval over a p-value is:

A. A confidence interval is easier to calculate
B. A p-value uses the standard deviation to calculate its value
C. Confidence intervals can assist the reader in assessing the magnitude of difference in effect between the intervention and control
D. A p-value uses the standard error of the mean to calculate its value

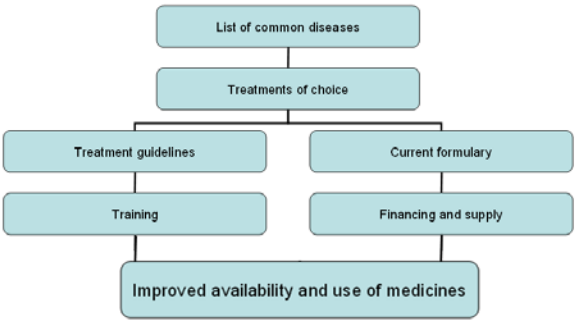
The formulary decision making process has three major steps

- Evaluate the Literature
- Compare to drugs on the formulary
- Get physician input

A drug formulary, or preferred drug list, is a continually updated list of medications and related products

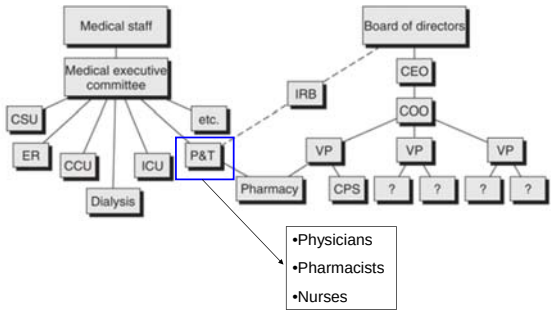
DRUG NAME	CROSS REFERENCE	DOSAGE FORMS	RESTRICTIONS
pravastatin	PRAVACHOL	Tablet: 10 mg, 20 mg, 40 mg	Restricted to patients on coumadin, protease inhibitors, cyclosporine, or other medications impacted by the cytochrome P450 enzyme system.
PLAVIX	clopidogrel		
itraconazole	SPORONOX	Capsule: 100mg	Restricted to valley fever and ID specialists.
EPOGEN	epoetin alfa	Covered strengths: 4,000 units/ml; 10,000 units/ml; 20,000 units/ml	

The goal of the formulary system is to provide a decision-making process leading to the selection of medications necessary for the treatment of any disease states likely to be seen in that institution.



The P&T meeting are where decisions are made

A P&T committee is usually a medical staff entity and, perhaps, only one or two pharmacists may actually be members of the committee



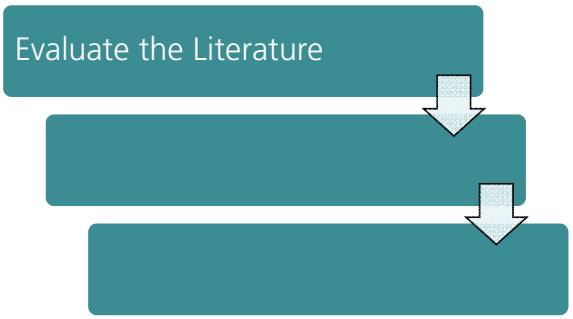
The purpose of a P&T committee is to promote safe, effective, and cost-effective drug therapy

- Determine what drugs are available
- Who can prescribe specific drugs
- Approve policies and procedures regarding drug use
- Quality assurance activities (e.g., DUR, medication usage evaluation, ADRs, medication errors

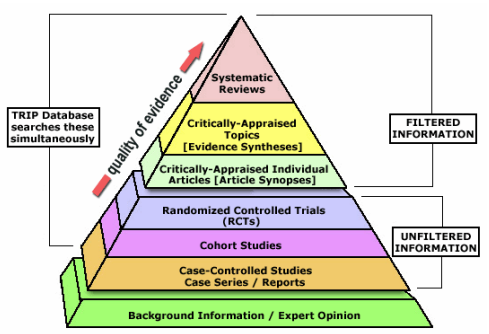
Pharmacists Should Be Proactive in Supporting a Pharmacy and Therapeutics Committee

- Evaluating medications for formulary adoption or deletion
- Preparing policies and procedures
- Communicating information from the P&T committee to other areas of the institution
- Creating hard copy and electronic versions of the formulary

Step 1



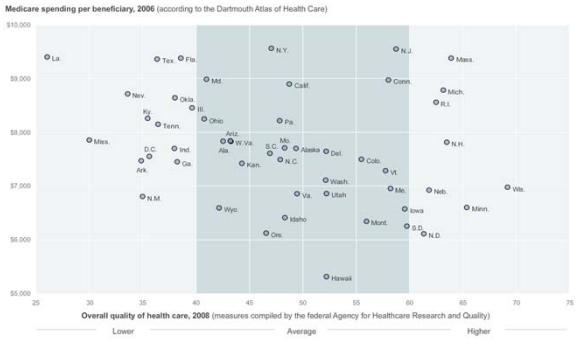
The recommendation must be supported by the evidence



The drug evaluation monograph reviews the major features of a drug product

- Efficacy
- Harms
- Cost
- Comparative effectiveness research

Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.



Correctly interpreting the p-values is crucial in evaluating a controlled clinical trial; not all statistically significant p-values are clinically important.

Efficacy of Antidepressant X: Change in HAM-D	
Decrease in score	P value
10	<0.001
10	<0.05
10	<0.005
20	<0.0411
20	<0.0001
20	<0.05

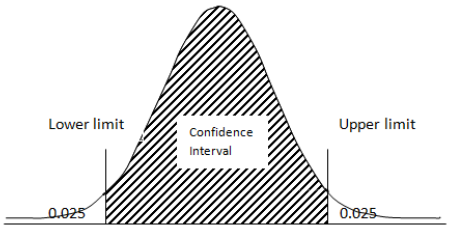
Statistical significance does not automatically clinical significance

Big Studies Make Small Differences "Significant"*

SIZE, n (IN EACH GROUP)	WEIGHT LOSS		MAIN EFFECT	P VALUE	APPROPRIATE CONCLUSION
	GROUP A (INTERVENTION)	GROUP B (CONTROL)			
10	20 lb	3 lb	17 lb	0.07	Not significant, but promising
1000	5 lb	3 lb	2 lb	0.03	Significant, but clinically unimportant

The use of 95% confidence intervals

- It is the range of values, consistent with the data, that is believed to encompass the actual or "true" population value



Determining if a result is clinically relevant

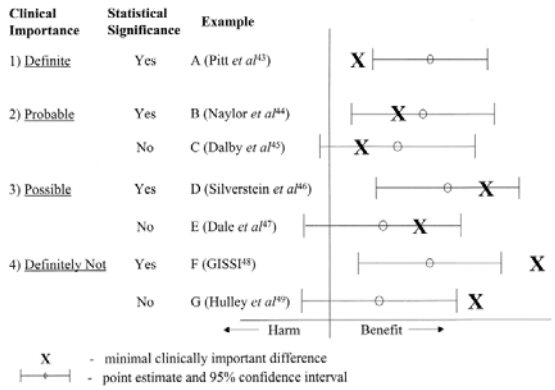
- Is a clinically relevant difference defined?
  - Clinical guidelines, previous studies
- Does it bring the study population in the normal range?
  - BP, A1c
- Is the outcome directly related to decreasing morbidity and/or mortality or is it a surrogate outcome?
- It is a direct measure or a surrogate outcome?

Efficacy of Antidepressant X: Change in HAM-D

Decrease in score	Average Baseline Score	% decrease in score	P value
10	30	33%	<0.001
10	20	50%	<0.05
10	40	25%	<0.005
20	40	50%	<0.0411
20	50	40%	<0.0001
20	25	80%	<0.05

95% CI examples

- HCTZ 6.25 mg lower SBP 4 mm Hg (95% CI=2 to 6) compared to placebo
- The difference in PFTs between groups was 0.51 L/min (95% CI= 0.23 to 0.79)
- The odds ratio of incidence of stroke for smokers compared to nonsmokers is 4.2 (95% CI= 1.32 to 14.22)



Situations when the 95% is not statistically significant

- When a 95% CI for a different includes zero
  - The difference in PFTs between groups was 0.51 L/min (95% CI= -0.12 to 0.79)
- When a 95% CI for a odds ratio or a risk ratio includes one
  - The odds ratio of incidence of stroke for smokers compared to nonsmokers is 4.2 (95% CI= 0.77 to 14.22)

Situations when the 95% CI is may not be clinically significant

- When the CI is wide
  - HCTZ 25 mg lowered SBP 20 mm Hg (95% CI=2 to 100) compared to placebo
- When the CI does not contain clinically relevant values
  - HCTZ 6.25 mg lowered SBP 2 mm Hg (95% CI=1 to 3) compared to placebo

Efficacy of Antidepressant X: Change in HAM-D

Decrease in score	Average Baseline Score	% decrease in score	P value	95% CI
10	30	33%	<0.001	4 to 12
10	20	50%	<0.05	9 to 13
10	40	25%	<0.005	2 to 11
20	40	50%	<0.0411	8 to 21
20	50	40%	<0.0001	12 to 32
20	25	80%	<0.05	18 to 24

Term and Definition	Abbreviation	Formula
Absolute risk reduction: the absolute arithmetic difference (ignore plus and minus signs) in rates of bad outcomes between the experimental and control groups	ARR	[EER − CER]
Number needed to treat: the number of patients who need to be treated to obtain 1 additional good outcome for a patient that would not have occurred without the treatment	NNT	1/ARR
Absolute risk increase: occurs when more patients in the experimental group develop the bad outcome compared with the control group	ARI	CER − EER
Number needed to harm: the number of patients that, if they were given the experimental treatment, would result in 1 additional patient being harmed compared with patients in the control group	NNH	1/ARI

EER indicates experimental event rate; CER, control group event rate.

Welk DS. How to read, interpret, and understand evidence-based literature statistics. Nurse Educ. 2007 Jan-Feb;32(1):16-20.

Using the number needed to treat to help in the formulary decision making process

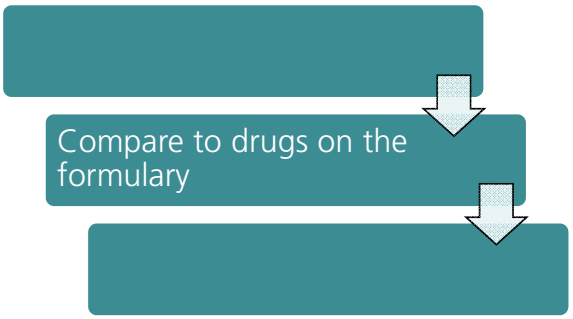
Table 1. Six hypothetical trials showing variation of NNT with absolute event rates*

Trial	Number of patients with outcome		EER (%)	CER (%)	RR	AR increase (%)	NNT
	Active	Placebo					
1	800	360	80	36	2.2	44	2.3
2	400	180	40	18	2.2	22	4.6
3	200	90	20	9	2.2	11	9.1
4	100	45	10	5	2.2	5	18.2
5	50	23	5	2	2.2	3	37.0
6	20	9	2	1	2.2	1	90.9

* Trials with 1,000 patients each given active treatment or placebo

AR: absolute risk; CER: control event rate; EER: experimental event rate; NNT: number needed to treat; RR: relative risk

Step 2



Use a standard system to compare it against other formulary agents: efficacy

Patient important outcome	
Prevention or cure of disease	3
Improve function (slow disease, alleviate symptoms)	2
End-of-life care	1
Medication tolerability	
Tolerable	
Evaluated medication as tolerable or more tolerable than comparator	2
Incidence of discontinuation of evaluated medication <10% (no comparator)	2
Low tolerability	
Evaluated medication less tolerable than comparator	0.5
Incidence of discontinuation of evaluated medication ≥10% (no comparator)	0.5

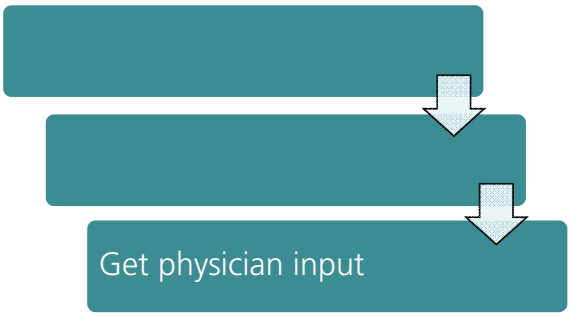
Use a standard system to compare it against other formulary agents: literature

Level of evidence	
Randomized trials assessing patient important outcome	3
Well done observational studies assessing patient important outcome	2
Other observational studies, expert opinion, unsystematic observations	1
Outcome duration	
>3 y	3
1–3 y	2
3 mo to <1 y	1
<3 mo	0

Use a standard system to compare it against other formulary agents: risks

1. The ordering and prescribing of this medication is restricted by an Food and Drug Administration mandate or manufacturer controls.	26
2. The labeling for this medication includes a black-box warning.	15
3. Historic Christiana Care experience with similar medications suggests there would be safetly concerns if the medication was approved for formulary addition.	10
4. This medication falls within the category of " high alert medication" as defined by Christiana Care policy.	10
5. This medication is dosed in a manner that increases the potential for error (e.g. weight-based dosing, titrated to effect, titrated in response to lab results, dosed in micrograms, etc.).	5
6. The drug interaction profile includes contraindications or major severity drug interactions with other medications currently utilized at Christiana Care.	3

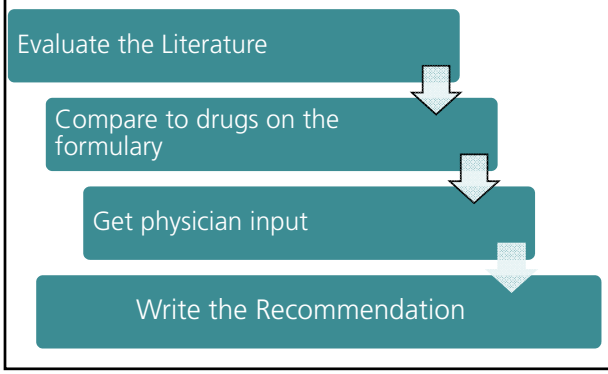
Step 3



Expert Physician Input is Valuable

- Complicated medical information gained by experience
- The physicians become part of the decision making process
- Decrease the chance of opposition because of "politics"

Putting it all together in the reommendation



The summary should contain the most important information about the drug

- Clinical Benefits:
  - The FDA-approved indication of the drug efficacy and effectiveness
  - Safety/tolerability
  - Shortcomings of current treatment and the unmet medical need that the proposed therapy addresses
- Economic Benefits
- Clinical Trial Conclusions

The recommendation must be clear, specific and actionable

- Added for uncontrolled use
- Added with restrictions
- Not added

Added for uncontrolled use

Added for monitored use

- Monitored use is occasionally needed if there is concern that a drug might be used in some inappropriate manner or has a great risk for adverse events.
- A limited drug usage evaluation would be conducted until it is evident that the drug is being appropriately used or not causing adverse events.
- One example where monitored use might be considered is an expensive biotechnology product that only has one normal dose, but multiple investigational doses, where it could be inappropriately prescribed without an investigational protocol.
- Also, a very toxic product might be monitored to see if the prescriber appropriately addresses adverse effects.

Prior Authorization is an Essential Managed Care Tool

- Addresses the Need for Additional Clinical Patient Information
- Promotes Appropriate Drug Use and to Prevent Misuse
- Administration of Step Therapy
- Administration of Quantity Management Rules
- Exception Process for Closed Formulary Benefits

Added with restrictions: Hospital examples

- Occasionally, there are drugs that should be added to a drug formulary, but are dangerous, or prone to misuse or overuse.
  - For example, the antineoplastics might be limited to prescriptions from oncologists or a defined group that might include a few physicians who are not oncologists (e.g., rheumatologists using methotrexate).
  - Often antibiotics may be restricted to a specific length of therapy, after which a new order must be written or the original order will automatically be discontinued.
- Other restrictions could include specific floors/areas of the institution or that the physician must receive counter-detailing by the pharmacist before the drug is dispensed.

Added with restrictions: managed care examples

- There may be a cap or limitation on the price, quantity, or on how many times a patient may receive a drug.
  - Prior authorization
  - Electronic step therapy: medications have to be tried before a specific agent may be available for coverage for a patient
  - Quantity limits
- These restrictions should be based on objective data, such as the FDA recommended maximum dose limitations or contraindications

Not added/deleted from formulary

- Less efficacy and/or more adverse effects
  - Alternatives on the formulary
- Cosmetic drugs
- Drugs not covered because of regulations
  - Medicare: Weight loss drugs
  - Carved out drugs: Must be billed to another service
  - OTC drugs

Guidelines to consider when making recommendations

- If the drug is less expensive or the same price as others, and is more efficacious or safer—add it to the formulary.
- If the drug is more expensive without added benefit, such as increased safety or effectiveness—do not add it to the formulary (or delete it from the formulary if it is already on it).
- The problem comes when the drug is more expensive and also has more benefits. In that case, the careful analysis of the literature and weighing of the institution's needs must be carried out. This is the gray area that has no right answer, but the most appropriate decision must be found.

Considerations when making recommendations

- National treatment guidelines
- Medical costs
- Prevalence
- Statistics
  - Confidence intervals
  - Number needed to treat
  - Number needed to harm

This is a conclusion, not a recommendation

- Ferriprox is an oral iron chelator that lowers serum ferritin and hepatic and cardiac iron stores in patients with thalassemia major and transfusion-related iron overload.
- Because of a lack of outcome studies, use should be limited to second-line therapy.
- Additional studies are necessary to establish a cardiac benefit relative to other iron chelation therapies.

This recommendation is clear, specific and actionable

- Ferriprox should be added with restrictions
  - Ferriprox was approved as a second line agent for chelation therapy
- Ferriprox should be used after Desferal or Exjade.
- Measure the absolute neutrophil count (ANC) before starting Ferriprox and monitor the ANC weekly on therapy
- Interrupt Ferriprox therapy if neutropenia develops (ANC < 1.5 x 10^9/L).
- Monitor ALT monthly during therapy with Ferriprox and consider interruption of therapy if there is a persistent increase in the serum transaminase levels.
- Interrupt Ferriprox therapy if ALT > 3x ULN.

1. Which of the following products is least likely to be reviewed by a Pharmacy and Therapeutics committee?

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