1   **The frequency of inappropriate non-formulary medication alert overrides in the inpatient**
2   **setting**

3

6 **Abstract**

7 **Background:** Experts suggests formulary alerts at medication order entry is the most effective

8 form of clinical decision support to automating formulary management.

9 **Objective:** Our objectives was to quantifying the frequency of inappropriate NFM alert

10 overrides in the inpatient setting and provide insight on how to better design formulary alerts

11 for automated formulary management.

12 **Methods:** The NFM alert overrides of 206 highest costing and most utilized NFM from 2012

13 were randomly selected for appropriateness evaluation. Using an empirically developed NFM

14 alert appropriateness algorithm, appropriateness of NFM alert overrides were assess by two

15 pharmacist via in-depth chart review. Appropriateness agreement of NFM alert overrides was

16 assessed with a Cohen's kappa. Exploratory analysis assessed which types of NFMs were most

17 likely to be inappropriately overridden, which type of override reasons was disproportionately

18 associated with inappropriate alert overrides, and what reasons explained why a NFM alert was

19 overridden inappropriate.

20 **Results:** Approximately 17.5% (n=36/206) of NFM alerts are inappropriately overridden. Non-

21 oral NFMs alerts are more likely to be inappropriately overridden compared to oral NFMs.

22 Alerts overridden with 'blank' reasons were more likely to be inappropriate. The failure to first

23 trial a formulary alternative is the most common reason for a NFM alert overridden

24 inappropriately.

25 **Conclusion:** Conservatively about one in five NFM alert overrides are overridden

26 inappropriately. Mandating an override reason for each NFM alert override and adding a list of

27   formulary alternatives to each NFM alert may decrease the frequency of inappropriate NFM

28   alert overrides.

Introduction

29

30   A hospital formulary is a list of medications agreed upon by hospital healthcare providers

31   for the care of admitted patients.[1] Medications on this list are often the cost-effective option

32   compared to their non-formulary alternatives, also termed non-formulary medications (NFMs).

33   Typically, NFMs are not stocked and require special order entry and procurement procedures

34   by the prescriber and pharmacy prior to use. These special order entry and procurement

35   procedures increases labor cost ($15.94 to $23.34)[2-4] and can substantially delay NFM initiation

36   (10.6 hours).[3] NFMs are also error prone, because they are unfamiliar to hospital staff may be

37   misinterpret for the more familiar formulary medications.[5-8]

38   However, the need for hospitals to provide NFMs is inevitable. There are times when

39   admitted patients are stabilized on a pre-admission, chronic NFM and substitution with a

40   formulary alternative can induce harm. Experts suggests formulary CDS, at medication order

41   entry, in the form of a pop-up alert containing a list of formulary alternatives is the most

42   effective design in balancing the need of NFMs while limiting the ill-effects of formulary non-

43   compliance.[9] Empiric verification of this suggestion is limited. Analogous evidence can be drawn

44   from the more commonly used computerized alerts (drug-allergy, drug-drug interactions, drug-

45   disease contraindication, etc.), where studies have shown these alerts improve prescribing

46   behaviors, reduce prescribing errors, impact clinical outcomes, and decrease medication cost.[10]

47   However, these benefits have often been challenged by the high frequency of alert overrides

48   (49-96%).[11] Therefore, we are unsure if the aforementioned alerts benefits can be generalized

49   to formulary alerts.

50   To our knowledge there are no studies evaluating the appropriateness of NFM alert

51   overrides. Our experience suggests this may be attributed to the resource-intensive task of

52   creating appropriateness criteria for each NFM. In our previous study, we empirically developed

53   a 'general' appropriateness algorithm that institutions could adapted to evaluate the

54   appropriateness of their institution specific NFM alert overrides. We adapted this general

55   algorithm to our institution's NFM use policy and criteria and evaluated the appropriateness of

56   a random sample of NFM alert overrides.

57   **Methods**

58   *Setting*

59   Brigham and Women's Hospital (BWH) is a 793-bed academic medical center located in

60   Boston, MA and admits approximately 46,000 patients annually for a full range of inpatient

61   services, with the exception of pediatrics. Medications available for patient care are governed

62   by BWH's formulary. Inpatient medications are ordered through an in-housed developed

63   computerized provider order entry (CPOE) system inside Brigham Integrated Computer System

64   (BICS). Full details of BICSand the CPOE system are described elsewhere.[12] Formulary alerts

65   embedded in the CPOE system are used to automate formulary management. Upon order entry

66   of a NFM, prescribers are informed of its non-formulary status with three types of pop-up

67   alerts: 1) a 'soft stop' requesting the input of a free-texted override reasons, explaining the

68   rationale of formulary deviation, 2) an 'intermediate stop' requesting an override reason and

69   the identifying the specialist physician who approved the NFM for use, and 3) a 'hard stop'

70   stating the NFM is not available for use and prompting the prescriber to order the preferred

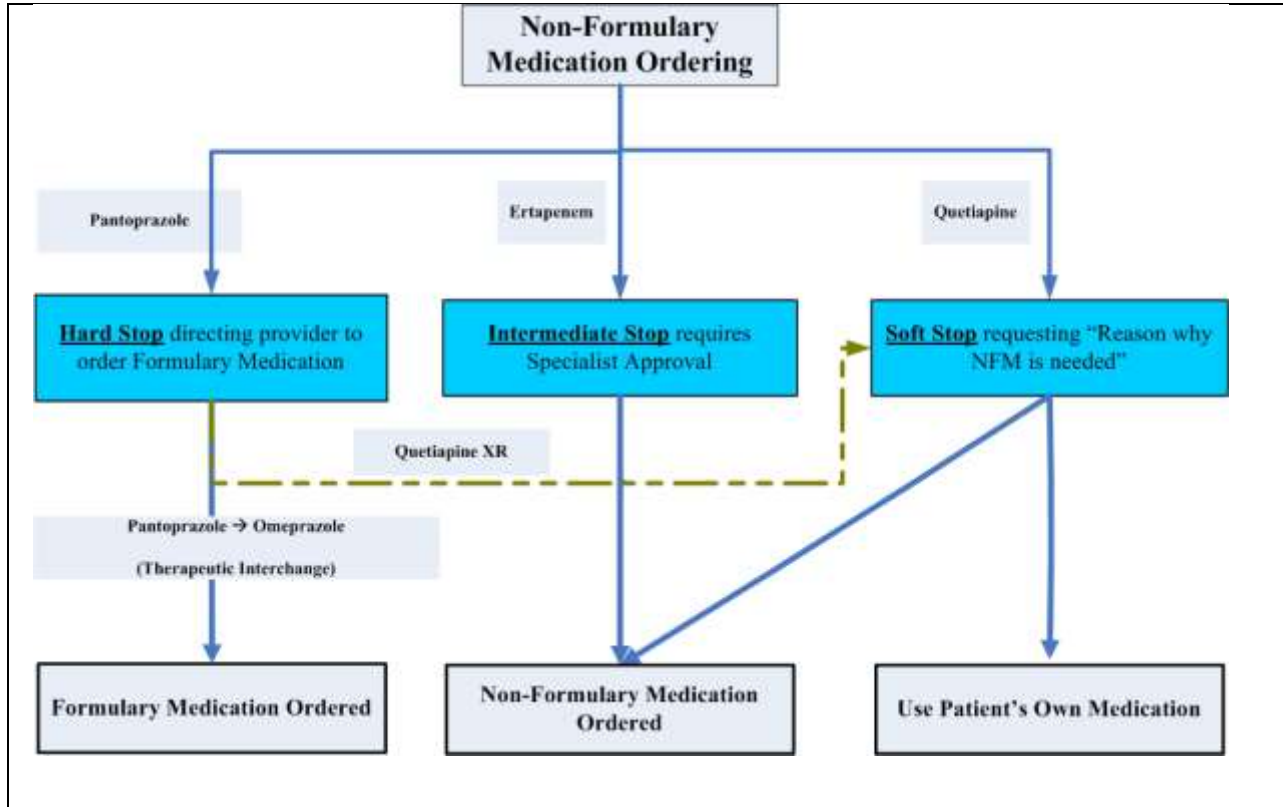71   formulary alternative **(Figure 1 and 2)**.

Figure 1: Non-formulary medication alerts

The dashed line represents the hard stop directing the prescriber to order a preferred NFM alternative. In this example Quetiapine XR cannot be ordered, but the hard stop directs the prescriber to order Quetiapine which is also NFM. The soft stop directs the provider to enter a reason why NFM is needed.

A.

```
                    NON-FORMULARY MEDICATION REQUEST
QUETIAPINE   PO

R
          This is a Non-Formulary drug.
          Please enter the reason(s) that this drug is needed:

         |




D

I            [    OK    ]              [  CANCEL  ]
P
2   Enter up to 4 lines of text.
    Press Enter on a blank line to end,  Esc to cancel
```
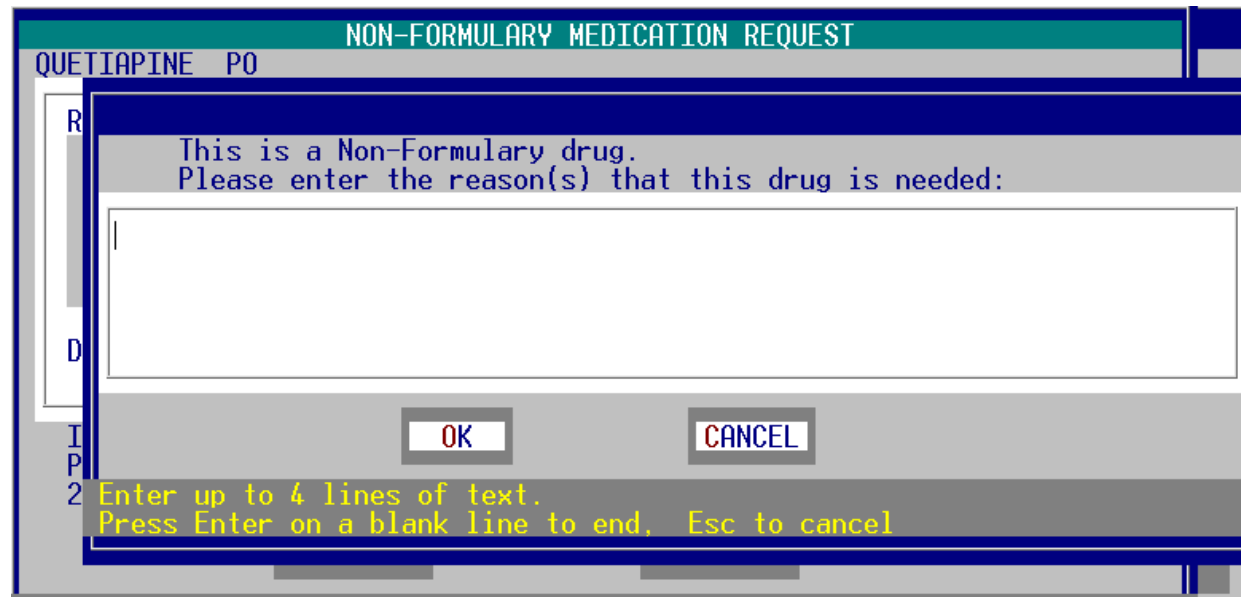
B.

```
                          MEDICATION ORDER
(*)New          Medication Name [ERTAPENEM SODIUM              ]
( )ChangE
( )D/C                   Route [IV        ]    [ ]Soundex   PAML Builder
```

```
      ERTAPENEM ALL ROUTES                      P&T NOTICE

 Please note! You have chosen a restricted antimicrobial which requires
 Infectious Disease Approval. If you have ID approval please enter the
 name of the approver when prompted.
 If you don't have ID approval, please page the Antibiotic Approval pager
 #22927 8am to 8pm to discuss.
 The Antibiotic Approval pager is unavailable 8pm to 8am pharmacy will
 dispense a 12-hr supply after review. Please page Antibiotic Approval
 pager #22927 after 8am tomorrow to discuss.


         order Ertapenem sodium              Cancel order
```

C.

Figure 2: Non-formulary pop-up alerts

A) Soft stop, B) Intermediate stop, and C) Hard stop

Study Design and Sampling of NFM alert overrides

73   The present study was an observational study of NFM alerts overridden from January 1st

74 to December 31st, 2012. These overrides and their relevant data elements were extracted from

75 BICS and loaded into a Microsoft Access Database (Microsoft Corp, Redmond, WA). Relevant

76 data elements included patient's medical record number, patient name, admission date,

77 discharge date, NFM order entry date, NFM order entry time, medication unique identifier,

78 generic medication name, route, dosage, dosing frequency, estimated number of doses

79 required, , prescriber name, prescriber unique identifier, and the free-texted NFM alert

80 override reason.

81   We limited our sample of NFM alert overrides to only original overrides and excluded

82 those that were the result of medication dose, direction, or frequency changes. The latter

83 overrides' rational for formulary deviation were often the same as the original and including

84 them into our evaluation would duplicate alerts. Further, at BWH there are two sources of non-

85 formulary designation, one in BICS and the other in an online formulary dictionary. Our internal

86 study found inconsistencies in these two sources. To ensure our evaluation included only true

87 NFMs, we further limited our overrides sample to medications listed as non-formulary in both

88 sources.

89   Total medication cost, composed of procurement and medication cost from 2009 to

90 2012, were computed for each NFM. The average procurement cost of providing a NFM over

91 formulary alternatives was estimated to be $20.07 per order.[2] This estimate was used to

92 convert the number of NFM orders to a monetary value. Medication costs were estimated from

93 a BWH's medication wholesaler account during the first quarter of 2014. NFMs were ranked

94   from highest to lowest total cost and twenty alert overrides were randomly selected from the

95   top 11 NFMs for alert override appropriateness evaluation. **Figure 3** describes our NFM alert

96   override sampling scheme.

```
┌─────────────────────────────┐
│   2012 NFM alert Overrides   │
│         (approvals)          │
│        N = 71,145            │
└─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐
│    Original NFM alert        │
│        Overrides             │
│        N = 59,102            │
└─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐
│       Top 11 NFMs'           │
│      Alert Overrides         │
│      N = 11,918$^{\psi}$     │
└─────────────────────────────┘
               │                    } Random selection of 20 alert overrides
               ▼
┌─────────────────────────────┐
│    NFM alert Overrides       │
│       N = 206$^{Y}$          │
└─────────────────────────────┘
```
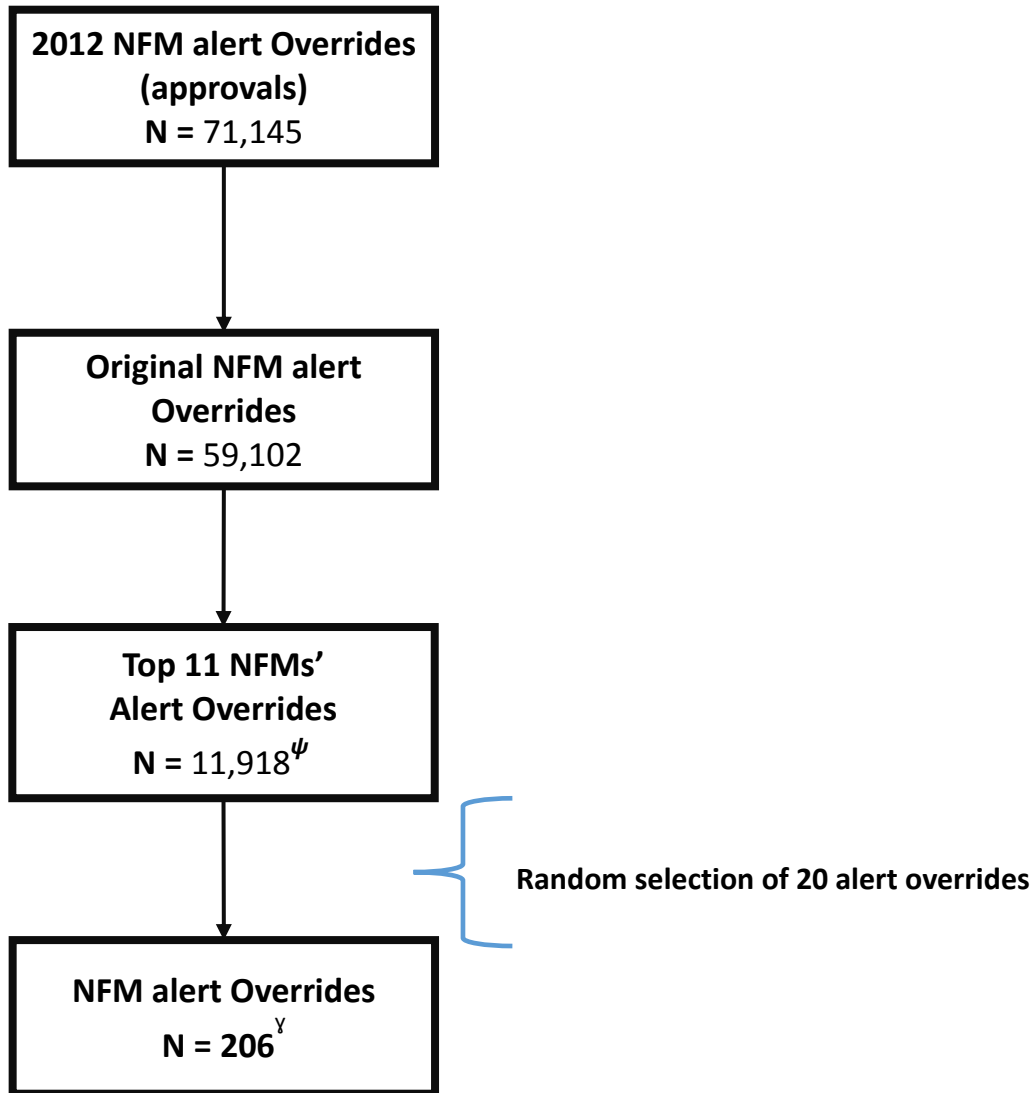
Figure 3: NFM alert override random selection
$^{\psi}$*Top 11 most approved and highest costing NFMs*
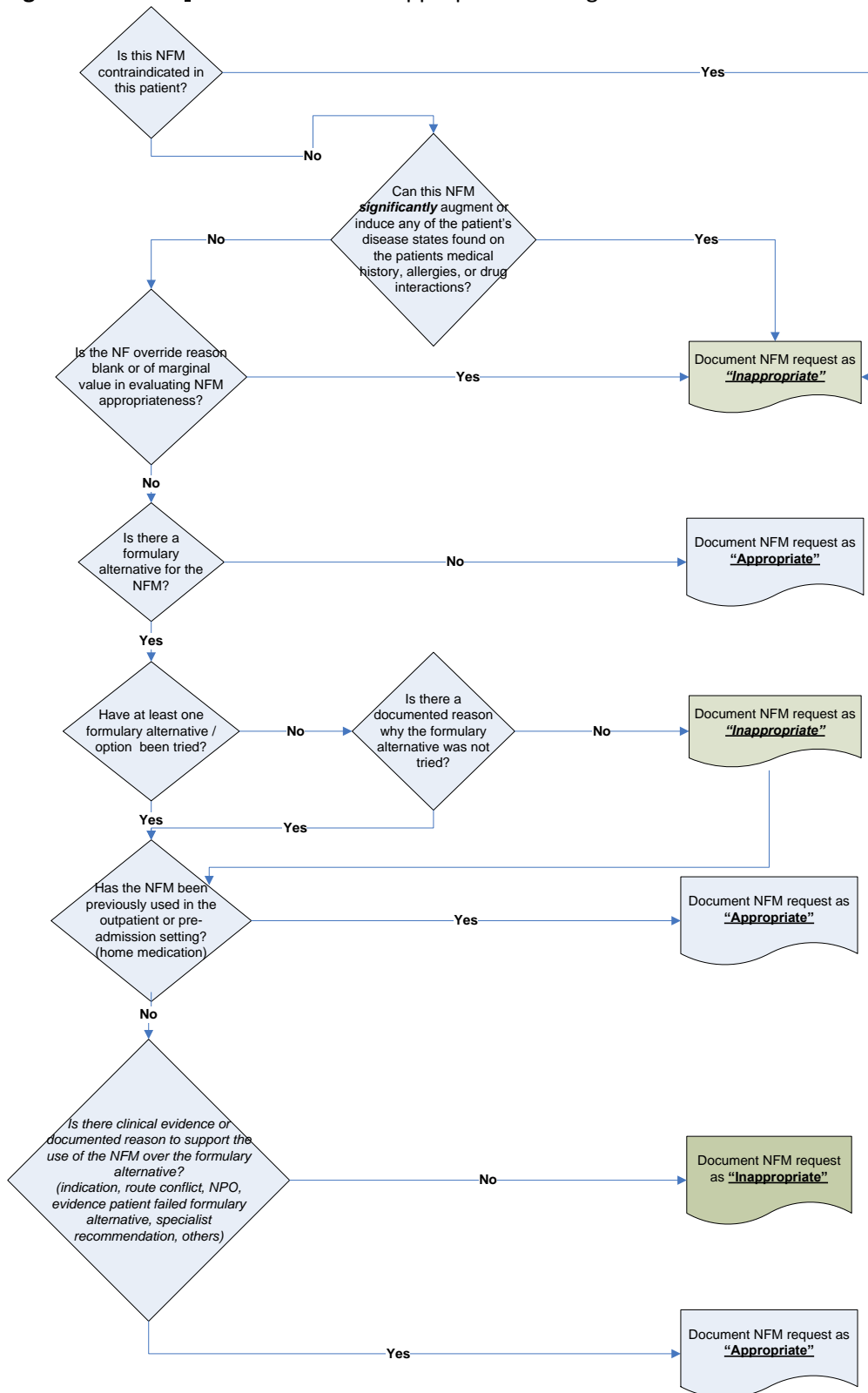^{Y}*In 2012 there were only six alert overrides for liposomal doxorubicin*

97

98   *NFM alert override appropriateness criteria*

99   Previously, we empirically developed a general NFM alert override appropriateness

100   algorithm from free-texted NFM alert override reasons. Full details of the methodology and

101   performance of the algorithm can be found elsewhere *(citation AJHP Study)*. In brief, a NFM

102   alert override reason categorization scheme was created from a random sample of 5,000

103   overrides according to keywords, context, and value explaining the rationale for formulary

104   deviation. A 30 question appropriateness algorithm was initially developed from these override

105   reason categories and presented to an interdisciplinary team of healthcare providers to

106   evaluate clinical creditability and for feedback. BWH inpatient pharmacist and pharmacy

107   administrators were also consulted on the NFM ordering process and the algorithm was

108   simplified to an eight question general appropriateness algorithm **(Figure 4)**. Available BWH

109   medication monographs, treatment guidelines and medication administration guidelines of the

110   top 11 NFMs were ascertained from the BWH Pharmacy intranet website and incorporated into

111   the general algorithm to create insitution specific NFM alert override algorithms.

112

Figure 4: General NFM alert override appropriateness algorithm

Is this NFM contraindicated in this patient?
— Yes →
— No →

Can this NFM *significantly* augment or induce any of the patient's disease states found on the patients medical history, allergies, or drug interactions?
— No →
— Yes →

Is the NF override reason blank or of marginal value in evaluating NFM appropriateness?
— Yes → Document NFM request as *"Inappropriate"*
— No →

Is there a formulary alternative for the NFM?
— No → Document NFM request as **"Appropriate"**
— Yes →

Have at least one formulary alternative / option been tried?
— No → **Is there a documented reason why the formulary alternative was not tried?**
   — No → Document NFM request as *"Inappropriate"*
   — Yes →
— Yes →

Has the NFM been previously used in the outpatient or pre-admission setting? (home medication)
— Yes → Document NFM request as **"Appropriate"**
— No →

Is there clinical evidence or documented reason to support the use of the NFM over the formulary alternative? (indication, route conflict, NPO, evidence patient failed formulary alternative, specialist recommendation, others)
— No → Document NFM request as **"Inappropriate"**
— Yes → Document NFM request as **"Appropriate"**

113

114   *Chart review and appropriateness evaluation*

115   An appropriateness evaluation interface was created in a Microsoft Access Form, where

116   all aforementioned relevant data elements were displayed. This was an attempt to mimic

117   formulary management at the at the point of care. All inpatient notes in "portable document

118   format" (PDF) corresponding to the hospitalization when the NFM alert was overridden was

119   downloaded from BICS and a hyperlink to this document was created in the Microsoft Access

120   Form to facilitate reviewer access. All medication orders, labs, and medication administration

121   logs during hospitalization were available through BICS. Outpatient medication records were

122   available through BWH's ambulatory care electronic medical record, Longitudinal Medical

123   Record (LMR).

124   Two pharmacists (QLH and MGA) assess the appropriateness of each NFM alert override

125   according to the institution specific NFM appropriateness algorithms via in-depth chart.

126   Generally, pharmacists first reviewed the override reason explaining the formulary deviation

127   and identified 'preliminary' formulary alternatives to the NFM. Second, the pharmacists

128   ensured that the NFM was not contraindicated or potentially induced any significant harm to

129   the patient according to the information found in the inpatient chart (i.e. chief complaint of

130   admission, medical history, allergies, or drug interactions). If the NFM posed any threat of

131   harming the patient, the NFM alert override was considered inappropriate. The reviewers also

132   reviewed medication orders and medication administration logs for evidence of trialing

133   formulary alternatives prior to the NFM alert override. The NFM alert override was considered

134   appropriate if a formulary alternative was first tried or documentation in the inpatient notes

135   reasonably explained why a formulary alternative was not an option, otherwise the NFM alert

136   override was inappropriate. Disagreements between pharmacists were resolved by discussion

137   with a third reviewer (DLS).

138   In our previous study, approximately one-half of all NFM alerts overrides were justified

139   with entered blanks and marginal value reasons (i.e. patient needs medication, patient

140   requires, attending prefers, etc.) *(AJHP citation)*. It is possible that these overrides are

141   appropriate, but justification was poorly documented. For example, there could be occasions

142   where specialist were consulted or formulary alternatives were thoroughly evaluated and

143   found to induced drug interactions, but the prescriber passively entered a 'blank' or marginal

144   value reason in the NFM alert override interface. Thus, 'blank' and marginal value reasons were

145   deemed inappropriate unless an appropriate justification (specialist consult, pharmacological

146   interaction, active disease that required the medication etc) for the NFM was discovered during

147   chart review.

148   Our previous study, we also found a significant number of NFM alert overrides were

149   justified with syntax variants of the NFM being a pre-admission or home medication. In these

150   cases the NFM alert override was considered appropriate only if the NFM was found active in

151   the LMR's electronic medication list during the dates of hospitalization. For NFMs justified by a

152   'disease or condition' reason, the literature was searched to ensure minimal supporting

153   evidence existed (at least a case-report) for the NFM's proposed indication. Any level of clinical

154   evidence found concluding effectiveness and citation of the 'disease or condition' in the

155   inpatient notes prompted these overrides to be deemed as appropriate. Remaining potential

156   reasons included specialist or pharmacist recommendation, therapeutic failure or intolerance

157   to NFMs, pharmacological reasons, end of life care, and drug shortages. NFM alerts overridden

158   with these reasons were appropriate as long as there was documented evidence in the

159   inpatient notes. For example, olanzapine was often justified with 'per psych recommendation,'

160   this NFM alert override would be considered appropriate if a psychiatrist consult

161   recommending the medication was existed in the inpatient notes prior the NFM being ordered.

162   *Outcomes and objectives*

163   Our primary objective was to quantify the frequency of NFM alerts overridden

164   inappropriately, computed as the ratio of NFM alerts overridden not according to our

165   appropriateness algorithms over the total number of overrides in our sample. Secondary

166   objectives included identifiying (1) which types of NFMs (oral and non-oral) were most likely to

167   be inappropriately overridden, (2) which category of NFM alert override reasons

168   disproportionately represent inappropriate NFM alert overrides, and (3) reasons explaining why

169   the NFM alert override was inappropriate. ***A post-hoc analysis was report the frequency of***

170   ***override reason given in NFM alert pop-up not congruent to the formulary deviation reason***

171   ***documented in the inpatient notes; we term these discrepancies as discordant override***

172   ***reasons.***

173   *Statistical Analysis*

174   Counts and frequencies were used to summarize the number of inappropriate overrides

175   according to our NFM alert override reason categorization scheme. Agreement in the

176   inappropriateness of NFM alert overrides between the two pharmacists was evaluated with a

177   Cohen's kappa. Fischer's exact test was used to compare the distribution of inappropriate NFM

178   alert overrides among oral and non-oral NFMs. A p-value of less than 0.05 was considered to be

179   statistically significant.

180   A Fischer's exact test was also first used to determine if inappropriate NFM alert

181   overrides were disproportionately distributed among the override reasons categories. *If the*

182   *exact test was found to be statistical significant (p-value < 0.05), the frequency of*

183   *inappropriate overrides in each override reason category was compared to the frequency of*

184   *the override reasons using a student t-test. A Bonferroni correction was applied to the student*

185   *t-test to adjust for multiple testing.* All statistical analyses were conducted using SAS software

186   (version 9.4 SAS Institute, Cary, NC). This study was approved by the Partners Human Research

187   Committee.

188   **Results**

Table 1

Top 11 Most Approved and Highest Costing NFMs	Number of NFM Alert Overrides	Inappropriate Alert Overrides	Frequency of Inappropriate Alert Override	Percentage of Total Inappropriate Alert Overrides
Oral non-formulary medications (n=80, 38.8%)				
Aprepitant (PO)	20	0	0.0%	13.9%
Olanzapine (PO)	20	0	0.0%	
Olanzapine ODT (PO)	20	1	5.0%	
Quetiapine (PO)	20	4	20.0%	
Non-oral non-formulary medications (n= 126, 61.2%)				
Dornase Alfa (Neb)	20	4	20.0%	86.1%
Liposomal Doxorubicin (IV)	6	0	0.0%	
Metronidazole 1% (Cream)	20	6	30.0%	
Mometasone Furoate (Inhaler)	20	4	20.0%	
Ranitidine (IV)	20	16	80.0%	
Rasburicase (IV)	20	0	0.0%	
Scopolamine (Patch)	20	1	5.0%	
Total	206	36	17.5%	100.0%

189

190   In 2012, 71,145 NFM alerts were overridden, of which 59,102 were original alert

191   overrides for 45,352 hospitalizations. Thus, about 1.3 original NFM alerts were overridden with

192   each hospitalization. The top 11 most approved and highest costing NFMs can be found in

193   **Table 1**. Four NFMs were oral medications, of which three were atypical antipsychotics. The

194   remaining seven included three intravenous medications, two inhalants, and two topicals. The

195   random selection scheme selected 206 NFM alerts overrides from these medications (there

196   were only six liposomal doxorubicin orders in 2012), which were prescribed by 174 distinct

197   health care providers: 150 physicians, 21 physician-assistants, and three pharmacists.

198   According to the appropriateness algorithms, the two pharmacists found 36 (17.5%)

199   NFM alerts inappropriately overridden **(Table 1)**. Agreement between reviewers was high,

200   κ=0.97 (95% CI: 0.92 – 1.00). Inappropriate alert overrides were disproportionately nested in

201   non-oral NFMs (p=0.007), where 86.1% (n=31) of inappropriate alert overrides were from non-

202   oral NFMs, while they constituted only 61.2% of the alert override sample **(Table 1)**.

Table 2: Non-Formulary Medication Alert Override Appropriateness Evaluation

Initiate Non-Formulary Override Reason Classification	Total Number (Percentage of Total)	Final Appropriateness Evaluation		
		Appropriate	**Inappropriate (Percentage of Total)**	**P-Value[1]**
Blank	**51 (24.8%)**	**31**	**20 (55.6%)**	*0.0001*
Disease or Condition Listed	**64 (31.1%)**	**60**	**4 (11.1%)**	*0.0004*
Home or Pre-Admission Medication	**38 (18.4%)**	**33**	**5 (13.9%)**	**0.4401**
Marginal Value for NF Decision:	**30 (14.6%)**	**26**	**4 (11.1%)**	**0.5204**
Acknowledge NF status	2 (1%)	2	0 (0%)	
Content Free	1 (0.5%)	1	0 (0%)	
MD/Attending/Team Request, Prefers NF Medication	11 (5.3%)	8	3 (8.3%)	
MisCommunication: Medication use direction	3 (1.5%)	3	0 (0%)	
Others	2 (1%)	2	0 (0%)	
Patient Preference/Request	2 (1%)	2	0 (0%)	
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1 (0.5%)	1	0 (0%)	
Reason Listed "Need/Requir* OR Patient Need*/Require**	8 (3.9%)	7	1 (2.8%)	
Pharmacological Reason:	**4 (1.9%)**	**3**	**1 (2.8%)**	**0.6908**
Contraindication	1 (0.5%)	1	0 (0%)	
Drug Route Conflict	1 (0.5%)	0	1 (2.8%)	
Others	2 (1%)	2	0 (0%)	
Specialist Recommendation	**10 (4.9%)**	**9**	**1 (2.8%)**	**0.4442**
Therapeutic Failure / Intolerant to formulary alternatives:	**9 (4.4%)**	**8**	**1 (2.8%)**	**0.6092**
Medication Listed	6 (2.9%)	6	0 (0%)	
Unspecified or Medication Not Listed	3 (1.5%)	2	1 (2.8%)	

Total	**206**	**170**	**36**	

[1]*P-values less than 0.007 (=0.05/7) were considered statistically significant, after application of a Bonferroni correction.*

203

204   There were 117 unique override reasons in the 206 NFM alert override sample. These

205   reasons were categorized into 17 of the 24 previously developed override reason categories

206   **(Table 2)**. The most common reason explaining formulary deviation was the provision of a

207   'disease or condition' (31.1%, n=64). No ('blank,' n=51) or marginal value reasons (n=30) were

208   provided in 39.4% of the alert override sample. 'Home or Pre-Admission Medications' reasons

209   were used to justify for 18.4% (n=38) and clinical reasons of pharmacological, specialist

210   recommendation, and failure or intolerance to formulary alternatives definition for only 11.2%

211   (n=23) of the NFM alert override sample.

212   Fischer's exact test confirmed a disproportionate distribution of inappropriate overrides

213   among the categories of override reasonsin our sample of alert overrides, p< 0.001. Specifically,

214   subanalysis found 55.6% (n=20) of inappropriate overrides were nested in the 'blank' override

215   reason category, while 'blanks' only accounted for 24.8% of all override reasons, p=0.0001.

216   Contrary, 11.1% of inappropriate overrides were nested in the 'disease or condition' reason

217   category, while these reasons accounted for 31.1% of the reasons in our sample, p=0.0004.

218   Statistical analysis did not find a disproportionate number of inappropriate overrides in the

219   remaining override reason categories **(Table 2)**.

220   Chart reviews identified 24 (66.7%) of the 36 inappropriate NFM alert overrides were

221   the result of not trialing formulary alternatives prior to the NFM **(Table 3)**. Eight (22.2%) of the

222   inappropriate NFM alert overrides were justified as a pre-admission or home medication, but

223   no evidence of active outpatient prescription was found in the patient's LMR. Chart reviews

224   also found no or limited information justifying the use of the NFMs in three (8.3%)

225   inappropriate overrides. These overrides were overridden with a 'blank' or marginal value

226   reason (prescriber preference). Lastly, there was one case where the NFM was deemed

227   clinically inappropriate to the patient involving the use of an atypical antipsychotic to address

228   dementia in an elderly patient, which has been linked to adverse outcome in chronic and as-

229   needed used.[13,14] Post-hoc analysis identified found 'blank' and marginal value reasons have the

230   highest frequency of discordant override reasons, 94.1% and 93.3%, respectively **(Table 4)**.

Table 3: Reasons explaining why the NFM alert override was considered inappropriate

Non-Formulary Alert Override Reason Class	Total	Formulary alternative was not first trial prior to NFM alert override	No citation or information could be found justifying formulary deviation during chart review	Clinically Inappropriate	No evidence of active home medication found in LMR	No documentation of specialist recommendation during chart review
Blank	20	17	1	0	2	0
Disease or Condition Listed	4	4	0	0	0	0
Home or Pre-Admission Medication	5	0	0	0	5	0
Marginal Value for NF Decision: MD/Attending/Team Request, Prefers NF Medication	3	0	2	1	0	0
Marginal Value for NF Decision: Reason Listed "Need*/Requir* OR Patient Need*/Require*	1	0	0	0	1	0
Pharmacological Reason: Drug Route Conflict	1	0	0	0	0	1
Specialist Recommendation	1	1	0	0	0	0
Therapeutic Failure / Intolerant to formulary alternatives: [Unspecified or Medication Not Listed]	1	1	0	0	0	0
Total	36	23 (63.89%)	3 (8.33%)	1 (2.78%)	8 (22.22%)	1 (2.78%)

231

Table 4: Frequency of Discordant NFM Alert Override Reasons

Initiate Non-Formulary Override Reason Classification	Total	Frequency of Discordant Reason for NFM Alert Override	Final NFM Override Reason Category (Post-Chart Review)							
			Blank	Disease or Condition Listed	Home or Pre-Admission Medication	Marginal Value for NF Decision: *MD/Attending/Team Request, Prefers, NF Medication*	Pharmacological Reason: *Drug Route Conflict*	Pharmacological Reason: *Others*	Specialist Recommendation	Therapeutic Failure / Intolerant to formulary alternatives: *[Medication Listed]*
Blank	51	94.1%	3	42	3	0	0	0	0	3
Disease or Condition Listed	64	7.8%	0	59	4	0	1	0	0	0
Home or Pre-Admission Medication	38	10.5%	0	1	34	0	0	0	3	0
Marginal Value for NF Decision:	30	93.3%	0	16	10	2	1	0	0	1
MisCommunication: Medication use direction	3	100.0%	0	2	1	0	0	0	0	0
Acknowledge NF status	2	100.0%	0	1	1	0	0	0	0	0
Content Free	1	100.0%	0	1	0	0	0	0	0	0
MD/Attending/Team Request, Prefers NF Medication	11	81.8%	0	7	2	2	0	0	0	0
Others	2	100.0%	0	2	0	0	0	0	0	0
Patient Preference/Request	2	100.0%	0	0	1	0	1	0	0	0
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1	100.0%	0	0	0	0	0	0	0	1
Reason Listed "Need*/Requir* OR Patient Need*/Require*	8	100.0%	0	3	5	0	0	0	0	0
Pharmacological Reason:	4	50.0%	0	1	0	0	1	1	0	1
Contraindication	1	100.0%	0	1	0	0	0	0	0	0
Drug Route Conflict	1	0.0%	0	0	0	0	1	0	0	0
Others	2	50.0%	0	0	0	0	0	1	0	1
Specialist Recommendation: Specialist / Other Service Recommended	10	20.0%	0	2	0	0	0	0	8	0

Therapeutic Failure / Intolerant to formulary alternatives:	**9**	**33.3%**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**8**
Medication Listed	6	0.0%	0	0	0	0	0	0	0	6
Unspecified or Medication Not Listed	3	33.3%	0	1	0	0	0	0	0	2
Total	**206**		**3**	**122**	**51**	**2**	**3**	**1**	**11**	**13**

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Discussion

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234   Our observational study found approximately one-fifth of NFM alerts at our institution are

235 inappropriately overridden. Non-oral NFMs alerts were more likely to be inappropriately

236 overridden compared to oral NFMs. We also found NFM alerts overridden with 'blank' were

237 more likely to be inappropriately overridden. Contrary, alerts overridden with 'disease or

238 condition' reasons are less likely to be inappropriately overridden. In-depth chart review found

239 the failure to trial a formulary alternative is the most common reason for a NFM alert override

240 to be inappropriate. Lastly, NFM alerts overridden with 'blank' or 'marginal value' reasons often

241 had justifiable formulary deviation reasons in the medical notes, but poorly documented in the

242 NFM alert pop-up interface.

243   To our knowledge there are no studies evaluating the appropriateness of NFM alert

244 overrides. This is likely attributed to the resource-intensive task of creating appropriateness

245 criteria for each NFM. Thus, we are unsure of how our findings compared to other institutions.

246 However, evaluating NFM alerts is inherently evaluating NFM use. Therefore, inappropriate

247 NFM usage frequencies may provide some estimation of the frequency of inappropriate NFM

248 alerts overrides*.*

249   Available studies suggest the frequency of inappropriate NFM usage is approximately 60%

250 to 70%. Specifically, a small 6-week prospective study at an academic medical center found 61%

251 of NFM use failed to comply to institution criteria[8] and a study evaluating the impact of a

252 comprehensive formulary management system from a no structured system decreased NFM

253 utilization from 17.8 to 5.9 medications per 100 admissions. This suggests an upper 67% bound

254   of inappropriate NFM use.[2] Our lower frequency is likely attributed to BWH's 'relaxed'

255   formulary and our sample was composed of NFMs previously approved by pharmacist for use,

256   hence also decreasing the number of inappropriate alert overrides.

257   The literature on formulary CDS is scarce. Our secondary findings provide important

258   perspective on the better design of these informatic tools for automated formulary

259   management. First, improvement in NFM alert systems should be prioritized to focus on non-

260   oral NFMs. Non-oral NFMs have greater formulary cost-implications than oral NFMs. Sweet et

261   al estimated the successful conversion of non-oral NFMs to a formulary alternative saves $7.04

262   to $94.60 compared to $16.62 in oral NFMs.[4] Our study found non-oral NFM alert overrides

263   more likely to be inappropriate compared to oral NFMs. Thus, optimization of automated

264   formulary management with non-oral NFMs is more likely to ensure formulary cost-savings.

265   Second, it is not surprising that the provision of no reason ('blank') to NFM alerts overrides

266   were disproportionately inappropriate. This is likely reflective of BWH's 'relaxed' formulary, but

267   also a characteristics volunteer free-texted alert system.[16] Mandating the provision of an

268   override reason may decrease the frequency of inappropriate NFM alert overrides.

269   Third, we expected NFM alerts overridden with clinical reasons (pharmacological, specialist

270   recommendation, and therapeutic failure / intolerant to formulary alternatives) to be more

271   likely appropriate, but was only able to demonstrate this relationship with alerts overridden

272   with 'disease or condition' reasons. The inability to demonstrate this hypothesis with the

273   former clinical reasons is likely due to their small numbers in our sample. Our previous study

274   found clinical reasons were rarely entered into our alert system *(cite AJHP study)*, which is

275   surprising with our sampling being composed of only approved NFM overrides. Chart review

276   found nearly all 'blank' (45 of the 51) and 'marginal value' (28 of the 30) reasons were of clinical

277   reasons and potentially appropriate in our post-hoc analysis **(Table 4)**. Thus, mandating the

278   provision of any override reason is likely to increase the frequency of alerts overridden with

279   clinical reasons, inherently decreasing the frequency of inappropriate NFM alert overrides.

280   Fourth, chart review found inappropriate NFM alert overrides were largely attributed to

281   prescriber not trialing formulary alternatives prior to the NFM. This is likely due to BWH's large

282   number of NFMs managed by a soft stop, where guidance to formulary alternatives is not

283   provided. Listing formulary alternatives in the pop-up alerts is likely to facilitate the use and

284   trial of formulary alternatives, hence decreasing the frequency of inappropriate NFM alert

285   overrides. A recent study found an obtrusive, hard-stop, pop-up alert prompting formulary

286   interchange decreased non-formulary non-adherence by 65%.[17] In addition a list of formulary

287   alternatives that is clear, concise, and include links to additional information may further

288   decrease the frequency of inappropriate NFM alert overrides.[11,18-20]

289   *Limitations*

290   Our study has a number of limitations. First, our study was retrospective and we limited

291   our review to the information documented in the inpatient medical notes. There were three

292   'blank' overrides where no citation or information regarding the rationale of NFM use was

293   found in the inpatient notes. Contrary, there were numerous incidences where 'blank'

294   overrides were actually justified after chart review. This leads us to infer that potentially

295   prescribers could have discussed the rationale for NFM use with the team, specialist, or

296   rounding pharmacist, but failed to document appropriately in the NFM alert pop-up window.

297   Second, our study was undertaken at a single medical center with an in-house

298   developed COPE system and utilized appropriateness criteria specific to one institution. Thus

299   the results may not be fully generalizable to other institutions and medication ordering system.

300   Nevertheless, our findings provide important perspective on the design of computerized

301   formulary management systems and formulary-based CDS, which may further ensure formulary

302   cost-savings, quality of care, and medication safety. In addition, our study empirically applied a

303   previously developed general appropriateness criteria; thus the presented study may serve as a

304   model for future formulary-based CDS studies and generate more override appropriateness

305   evaluation.

306   Lastly, our analysis focused on only a subset of NFM alert overrides, the most approved

307   and highest costing NFMs. Thus, it remains unknown how our findings might have differ with

308   the inclusion of all NFMs. Yet such study is likely infeasible due to the need to create

309   appropriateness criteria for all NFMs. Our reasonable decision to focus on the highest cost and

310   most approved NFMs was to identify insight that may yield the greatest improvement in the

311   use of alerts for formulary management.

312   **Conclusion**

313   To our knowledge, our study is the first to empirically evaluate the appropriateness of

314   NFM alerts overrides in the inpatient setting. Evaluating the effectiveness of these overrides is

315   inherently evaluating NFM usage. This is a labor-intensive task and requires the creation of

316   appropriateness criteria for each NFM. We circumvented this issue by tailoring an empirically

317   developed NFM alert override general appropriateness algorithm to our institution's NFM

318   policy and use criteria and focused on the most approved and high costing NFMs. The present

319   study conservatively estimates that one in five NFM alert overrides is inappropriately

320   overridden and at minimum mandating an override reason for each NFM alert override and

321   adding a list of formulary alternatives to each NFM alert may decrease the frequency of

322   inappropriate NFM alert overrides**.**

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