This is a postprint of the article published as:
Larsen, L.K. et al. (2021). Complexity of drug substitutions caused by drug tenders: A mixed-methods study in Denmark. Hospital Pharmacy, 56(4), 314-320.

TITLE: Complexity of drug substitutions caused by drug tenders: A mixed-methods study in Denmark

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WORD COUNT: 3132

Abstract

Objective: The objective of this study was to investigate factors influencing the complexity of drug substitutions caused by drug tenders in a Danish hospital setting.

Methods: A sequential explanatory mixed-methods approach was employed. In the first phase, a custom-made, self-administered questionnaire was distributed to 58 pharmacists and pharmaconomists employed at the Hospital Pharmacy in the North Denmark Region. The questionnaire consisted of 13 questions which helped to obtain quantitative information on factors complicating drug substitutions. The results were used to inform the construction of an interview guide for a focus group interview held in the following qualitative second phase of the study. The focus group included 11 pharmacists and pharmaconomists from the Hospital Pharmacy in the North Denmark Region working with drug substitutions. The focus group interview was conducted to facilitate validation of results from the questionnaire survey and to add further perspectives on identified factors influencing the complexity of drug substitutions.

Results: Findings from both phases of the study revealed that implementation of drug substitutions is more complex when drug strength or pharmaceutical form of a drug changes, compared with changes of drug trade name or package size. Furthermore, it was established that anatomical therapeutic chemical classification codes could be used to identify drug substitutions that are typically complex, for example L01 and N05. Several external factors were also found to influence implementation of drug substitutions, e.g., related to drug usage, number of end users and hospital wards.

Conclusions: From a hospital pharmacy point of view multiple factors were identified that could influence and complicate the implementation of drug substitutions with different impact size. Those factors included both changed characteristics of drugs, anatomical therapeutic chemical classification codes involved in substitution, and external factors.

Keywords:
Drug substitution, generic substitution, pharmaceutical tendering, drug tender, hospital pharmacy, mixed methods, procurement

1. Introduction

Across the world, health care expenses are rising which indeed comprise increasing drug costs [1]. In Denmark, costs for hospital medicines have increased by 7.8% every year from 2007 to 2015 [2]. They are expected to rise even further in the future, causing heavy economic pressure on health care systems and urgent needs for optimized procedures to restrain costs [2–4]. In Denmark, tendering and procurement of medicine to public hospitals is a national task carried out by Amgros, a non-profit organization owned by the five Danish regions. The purpose of the shared tendering is to ensure that hospitals get the required medicines at the lowest possible cost [5–8].

The tendering process leads to drug substitutions when drugs are purchased from new suppliers, and the hospital pharmacies support the drug substitution implementation [9,10]. Efficient implementation is important in order to benefit from discounts achieved through tendering. However, substitution of drugs increases the risk of medication errors [11]. Therefore, the implementation process must not be limited to economic aspects but should also consider patient safety [12,13]. To the best of the researchers' knowledge, literature or guidelines on exactly how to assess the complexity of drug substitutions during implementation is still lacking.

Considering the lack of systematic procedural guidelines and consequences for efficient implementation of substituted drugs on economy and patient safety, this study aimed to investigate factors influencing the complexity of drug substitutions. This is an initial step to provide a more structured process of implementing drug substitutions, which may consequently facilitate a more objective and effective assessment procedure at hospital pharmacies, increasing patient safety in the long term.

2. Methods

A sequential explanatory mixed-methods approach was employed, consisting of an initial quantitative phase with a questionnaire survey, followed by a qualitative phase with conduction of a focus group interview (Figure 1). The study was conducted at the Hospital Pharmacy in the North Denmark Region (HPN) to investigate complexities from a hospital pharmacy point of view.

[Insert Figure 1]

2.1 Questionnaire survey

A questionnaire was developed based on internal instructions and previous experiences at the HPN, to obtain further knowledge on factors complicating drug substitutions and the extent of which they do. Respondents were selected based on purposive sampling, as the target population was employees experienced with implementation of drug substitutions, i.e. pharmacists and pharmaconomists.

Respondents were asked to rate the complexity of different drug substitutions on a numeric rating scale from 1 to 10, where 1 equaled "Not at all complicated" while 10 equaled "Extremely complicated". Along with every rating, comments could be added in a text box. The questionnaire was divided into four parts. The first part of the questionnaire concerned complexity of drug substitutions when different characteristics of a drug are changed, i.e. trade name, strength, pharmaceutical form and package size. In the second part, respondents were asked about which anatomical therapeutic chemical (ATC) classification codes they found complicated when involved in drug substitutions. Part three included assessment of

different circumstances present at drug substitution. The last part of the questionnaire involved demographic questions.

Before distribution of the questionnaire, pretesting was performed including four content experts, a potential respondent and a survey expert in order to qualify the questionnaire and ensure that wording and answering categories were concise and appropriate. The final questionnaire included 13 questions, and time estimation for completion was 10-15 minutes.

The questionnaire was distributed using SurveyXact (v12.8, Ramböll Management, Aarhus N, Denmark), through e-mail including a link, open for two weeks in October-November 2018. The respondents received two reminders during that period.

2.2 Focus group interview

A focus group interview was held in December 2018 (Figure 2). Participants were pharmacists and pharmaconomists employed at the HPN. The participants were invited based on purposive sampling, as experience in handling drug substitution implementation was needed. An interview guide was designed based on results from the questionnaire survey. The aim with the focus group was to validate the findings in the survey and to facilitate discussion of drug substitution complexity when various drug characteristics changes. Furthermore, the focus group was asked to discuss whether they agreed on the variations in complexity which were established from the initial results.

Written informed consent was obtained to permit audio recording of the session and use of the generated data in subsequent analysis.

[Insert Figure 2]

2.3 Data analysis

Descriptive statistics were performed using SurveyXact and Microsoft Excel (Microsoft Office 365 ProPlus, v1809, Washington, USA). Frequencies were presented as percentages and descriptives as medians and interquartile ranges [Q1-Q3]. Flowcharts were designed using Lucidchart (Lucid Software Inc., Utah, USA). Statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS, v24, New York, USA). Statistical significance was considered for p-values ≤ 0.05. Normal distribution of data was tested using Shapiro Wilk's normality test.

Comparisons between assessments of changes in drug characteristics were performed using Friedman's test and post hoc analysis with Wilcoxon's signed rank test, and Bonferroni correction was applied to detect significant differences. A two-way mixed ANOVA with pairwise comparisons was used to compare assessments of drug characteristic changes between employees from different departments.

The qualitative data analysis involved transcription of the audio recording to obtain written data for analysis. The transcript was read through and codes were identified. Subsequently, the transcript was coded assisted by NVivo 12 (QSR International, Melbourne, Australia). Codes were clustered into categories based on the discussed issues and how the various factors influence the complexity of drug substitutions.

3. Results

The questionnaire was distributed to 58 employees at the HPN, and 35 completed questionnaires were returned, yielding a response rate of 60%. One respondent was excluded, due to comments about lacking drug substitution knowledge. Out of 34 respondents included for analysis, 16 (47%) worked in the clinical pharmacy department, 14 (41%) in the medicine information department, 3 (9%) in the logistics department and 1 (3%) in the department for production of cytostatics.

In the focus group interview 11 employees participated, including 8 (73%) from the medicine information department, and 3 (27%) from the clinical pharmacy department.

3.1 Complexity of drug characteristic changes in drug substitutions

Change of drug strength (median=7.50 [6.00-9.00]) and pharmaceutical form (median=7.00 [5.25-9.00]) were rated more complicated than change of trade name (median=5.00 [2.25-7.75]) and package size (median=2.50 [2.00-4.00]). Friedman's test yielded significant differences between the assessments ($p<0.001$) (Figure 3-A) and post hoc analysis revealed significant differences between ratings of single changed characteristics, except for between changed pharmaceutical form and strength (Difference between change of name and strength: $p<0.001$, name and pharmaceutical form: $p<0.001$, name and package size: $p=0.002$, package size and pharmaceutical form: $p<0.001$, package size and strength: $p<0.001$, strength and pharmaceutical form: $p=0.622$).

[Insert Figure 3]

The focus group supported the result that in general, change of pharmaceutical form or drug strength is more complex than change of trade name or package size. It was added that for change of strength, it is necessary to distinguish between change of the strength designation and of the strength itself, with the latter being more complex. It was also agreed that the complexity of changed pharmaceutical form depends on the particular forms being switched. The focus group agreed that the complexity of trade name change depends on the specific drug in question, how familiar nurses are with the name, and how frequently the drug is used. For change of package size, the low complexity rating was explained by the change not influencing patient safety.

Although not significant ($p=0.116$), the assessments of changed trade name was rated more complex by employees from the clinical pharmacy department (median=5.00 [3.00-7.00]) than the medicine information department (median=3.00 [2.00-5.00]). The department for production of cytostatics and the logistics department were not included, because of low numbers of respondents. At the focus group, it was proposed that the tendency of a difference in assessments of trade name change between the departments originated in different perspectives. For example, the clinical pharmacy department frequently experience the challenges nurses have with remembering and recognizing new trade names.

In cases where two characteristics changed simultaneously (Figure 3-B), change of strength and pharmaceutical form were rated most complicated (median=9.00 [8.00-10.00]), while concurrent change of trade name and package size was rated the least complicated (median=5.00 [3.00-6.00]). With three and four characteristics changing simultaneously, the ratings accumulated in the higher end of the complexity scale (Figure 3-C/D).

Additional changes in drug characteristics that might potentially increase the complexity of drug substitutions were listed at the focus group, e.g., concerning changes in taste, storage conditions, color and packaging. It was also elaborated that change of device is complex because it requires end user training.

3.2 Complexity of specific ATC codes in drug substitutions

The respondents of the survey were asked how complicated they would rate drug substitutions when concerning specific ATC codes outlined at the second level of the ATC code (Table 1). In cases where respondents commented that they did not know the listed ATC code, they were excluded from analysis. One respondent indicated that L01 was highly complex due to the expensiveness of drugs with this classification.

ATC subgroup	Complexity rating (1-10)			
	Median	Q1-Q3	Minimum	Maximum
L01: Antineoplastic agents	8.00	6.50-9.00	3.00	10.00
N01: Anesthetics	7.50	5.00-8.00	2.00	9.00
B05: Blood substitutions and perfusion solutions	7.00	6.00-7.75	4.00	9.00
J06: Immune sera and immunoglobulins	7.00	5.00-8.00	2.00	9.00
J01: Antibacterial agents for systemic use	6.00	5.00-7.75	2.00	9.00
A10: Antidiabetics	5.00	3.00-7.00	2.00	9.00

The most frequently mentioned ATC codes to be complex were L (Antineoplastic and immunomodulating agents), N (Nervous system) and J (Anti-infectives for systemic use). In the case of ATC code N, three respondents commented that drug substitutions are more complex when involving drugs for psychiatric patients and this was also agreed on in the focus group. Furthermore, the ATC code L was also agreed by the focus group to be very complex, as the expensiveness of drugs in this group increases the pressure on the employees to ensure successful and fast implementation. It was also added by the focus group that drug substitutions require additional focus when involving drugs for specific patient groups such as neonatal patients and children. A summary of main results is provided in figure 4.

[Insert Figure 4]

4. Discussion

This study showed that several factors influence the complexity of the process and outcome of implementing drug substitutions in Danish public hospitals. Some aspects are critical because of the direct risk on patient safety. Others are complicated because additional resources are needed to ensure successful and rapid implementation; thus, concerning economic aspects. The results of factors complicating drug substitutions identified through the two study phases are discussed in the following sections.

4.1 Change of drug strength and pharmaceutical form

Change of drug strength and pharmaceutical form were determined more complicated than change of trade name and package size. Although change of strength designation was specified less complex than change of the strength itself, it was illustrated by *Becker et al.* that such change may have serious consequences. They reported a case where changes in strength designation for dexamethasone ampoules caused administration of wrong dose, because nurses were not aware of the change [14]. Therefore, changed strength designation should still be given extra attention during substitution. The complexity of change of both strength designation and change of the strength itself depends on the pharmaceutical form in question, possibly because of differences in the difficulty of calculations required to identify the right dose. This may result in extra time required for health care staff to secure correct dispensing, which *Håkonsen et al.* also considered an important issue during drug substitutions [12].

The results indicated that the complexity of change of pharmaceutical form should be graded in further details, as it depends on the specific pharmaceutical forms being switched. The focus group agreed that change between tablets and capsules is less complex than change from solution for injection to powder for injection solution. This might be due to the increased workload when nurses prepare the medication, as additional steps in the dispensing process equals further resources required for the overall medication process.

4.2 Change of trade name

The estimated complexity of trade name change varied considerably between respondents. The focus group explained the variation by the fact that for some drugs, trade name change was not an issue, while for others trade name change had been very complicated. The complexity might depend on whether the name of a new drug resembles the old one, which makes it easier to learn the new name, and this would consequently decrease the time consumed to identify a substituted drug in the inventory. However, a new name similar to that of another drug in the inventory, may potentially increase the risk of medication errors. This was established by *Håkonsen et al.* where nurses consulted in their study expressed that similar new drug names were an essential issue, and an important risk factor frequently associated with medication errors during substitution [12].

In the focus group discussion, it became evident that the complexity of a trade name change depends on whether the health care staff uses the generic or the trade name. This is supported by an example provided by *Becker et al.* where only the trade name and not the generic name was printed on the primary packaging [14]. In this case, health care staff was used to the generic name, and that caused the problem when the staff were required to identify the correct drug for dispensing. This is a suitable illustration to emphasize that if health care staff does not use the generic name, new trade names can cause problems in the substitution process.

Prescription of drugs by their generic names has been proposed a solution to reduce the frequency of medication errors caused by drug name confusion [12,15,16]. This would potentially help health care staff to get familiar with the generic name instead of trade name, leading to easier identification of drugs after substitution. However, disadvantages also have to be considered. As established by *Hellebek et al.,* generic names are often difficult and harder to get familiar with [15]. Additionally, some drugs might not be qualified for generic prescribing, because of potential therapeutic inequivalence of drugs [15,16].

4.3 Change of package size

Of the drug characteristics specifically consulted, change of package size was determined the least complex change to implement. This was related to the concept that change of package size influences economic aspects and does not directly influence patient safety. Therefore, such change requires less focus during implementation than change of other characteristics. For drug substitutions in general, aspects of both economy and patient safety must be considered. However, it seems reasonable that changes not directly influencing patient safety are less complex, because they do not entail just as critical consequences. However, providing information about a change in package size might be beneficial to avoid issues with storage capacities or ordering of incorrect drug quantities, which can be associated with unintended costs.

4.4 Miscellaneous factors influencing complexity of drug substitutions

Factors increasing the complexity of drug substitutions might be possible to handle by providing information about changes prior to implementation. In some cases, however, there is no chance of preventing problems that first arise when the substitution is already implemented in the clinic. For instance, if changed primary packaging or color of a tablet causes confusion, so nurses have to spend time ensuring correct dispensing. Besides, the focus group agreed that change in storage conditions might also cause problems. This was demonstrated by *Becker et al.* who experienced a drug change where a drug suddenly needed to be stored in the refrigerator, but as the drug was used in emergency kits, this was not possible [14]. Such circumstances would inevitably expend resources to come up with a solution.

The current study showed that it is possible to identify ATC codes requiring additional focus during implementation. This applies e.g., for drugs with ATC codes N05 and N06, as they are typically used in psychiatry. This is supported by *Carroll*'s study, describing that substitutions in psychiatric patients may be difficult, because they are more suspicious when drug changes occur [17]. L01 is another ATC code where complex substitutions often happen, partly due to the high cost of these drugs, meaning that great savings are often associated with such substitutions. Therefore, employees must work fast to provide sufficient information to affected parties and adjust stocks accurately on point. Substitution of drugs used for children and neonatal patients was also found to increase complexity, and this is supported by *Becker et al.* who established that changes in preservatives in drugs used for children could cause problems because of risk of toxicity [14].

The results of the present study clarified that rather external factors may also complicate drug substitutions, e.g., including the number of wards a drug substitution is implemented at. Highly complex drug substitutions might not be that complicated if they are only implemented at one hospital ward, while other substitutions that initially seem simple, might turn out to be complex to implement if many wards have to be informed. Lastly, it seemed to matter whether a ward frequently experiences drug substitutions or not. *Håkonsen et al.* found that 75% of nurses included in the study found the frequent drug substitutions problematic, and the nurses felt insecure about the substitutions [12]. This highlights the importance of informing wards about drug substitutions, so they are always prepared for changes. It remains to be investigated exactly how information to the clinic is provided in the most effective way.

4.5 Limitations and strengths

Use of questionnaires entails the risk that questions are not understood the way the researcher intended and social desirability [18]. Therefore, pretesting of the questionnaire was carried out. Some respondents commented that it was hard to fill out the questionnaire, and further tests before distribution might have increased the response rate.

In the current study, 11 employees participated in the focus group interview. A large group can be a limitation, because some participants will dominate the discussion, while others stay quite because of big group size. However, this was not encountered in the focus group discussion in the current study, and the large group only provided further perspectives on the research topic.

4.6 Conclusion

The current study established that specific ATC codes and changed characteristics of drugs increase the complexity of implementation with different impact size. Based on the findings, a system for categorization of drug substitutions could be applied in the assessment process, ultimately ensuring a continuously high level of patient safety.

Acknowledgements

The authors thank all employees at the Hospital Pharmacy in the North Denmark Region for their time and dedication to participate in the study and contribution with their valuable knowledge and experience in the field.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Legends

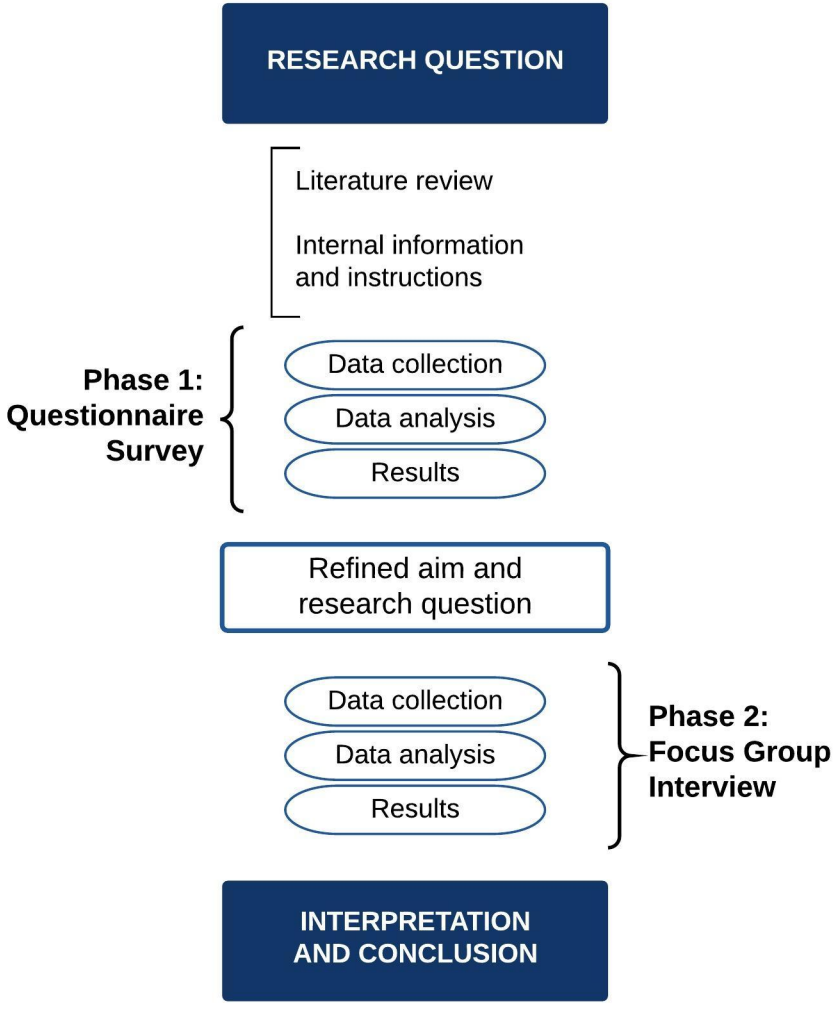
Table 1: Ratings of complexity of ATC codes. Q1: First quartile, Q3: Third quartile.

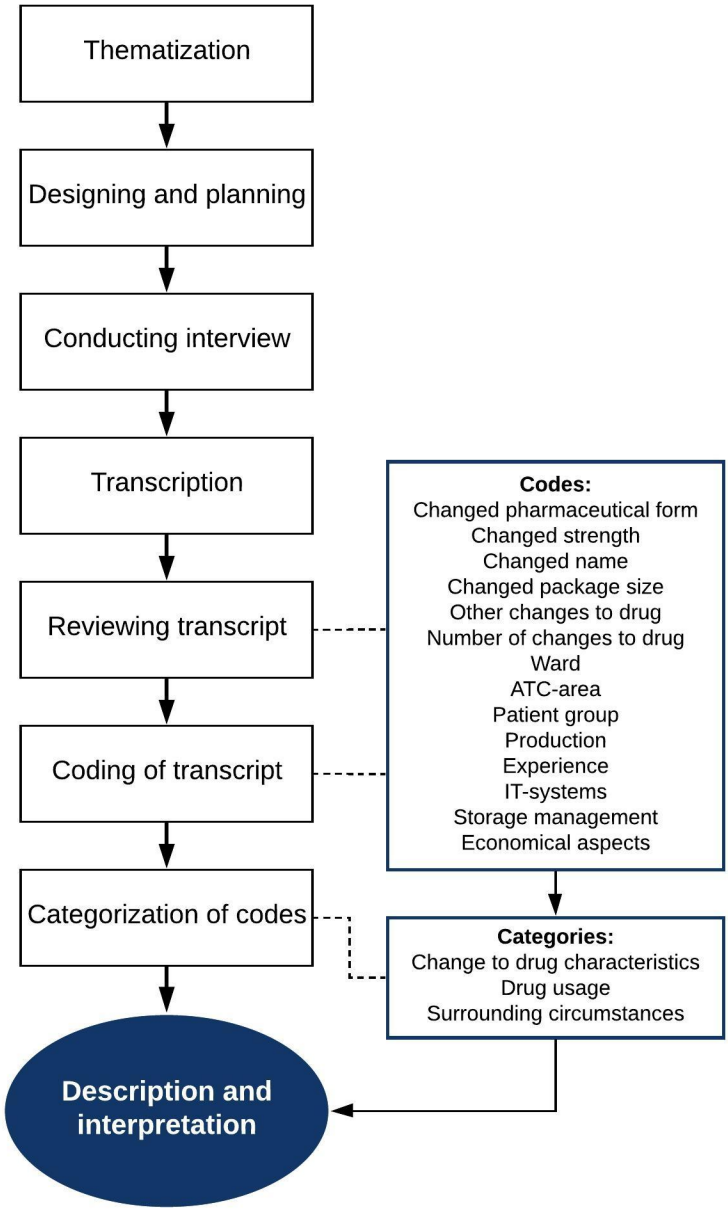
Figure 1: Mixed methods applied in the study.

Figure 2: Workflow of designing, performing and analyzing the interview in phase 2 of the study.

Figure 3: Boxplots illustrating ratings of complexity of drug substitutions with A) 1, B) 2, C) 3 and D) 4 changed characteristics (n=34). n.s.: not significant, *: p≤0.008, **: p≤0.0016, ***: p≤0.00016 (Significance level at 0.05 with Bonferroni correction applied).

Figure 4: Summary of main findings from the quantitative phase 1 and the subsequent qualitative phase 2 of the study.


RESEARCH QUESTION
Literature review
Internal information and instructions
Phase 1: Questionnaire Survey
Data collection
Data analysis
Results
Refined aim and research question
Data collection
Data analysis
Results
Phase 2: Focus Group Interview
INTERPRETATION AND CONCLUSION


Thematization
Designing and planning
Conducting interview
Transcription
Reviewing transcript
Coding of transcript
Categorization of codes
Description and interpretation
Codes:
Changed pharmaceutical form
Changed strength
Changed name
Changed package size
Other changes to drug
Number of changes to drug
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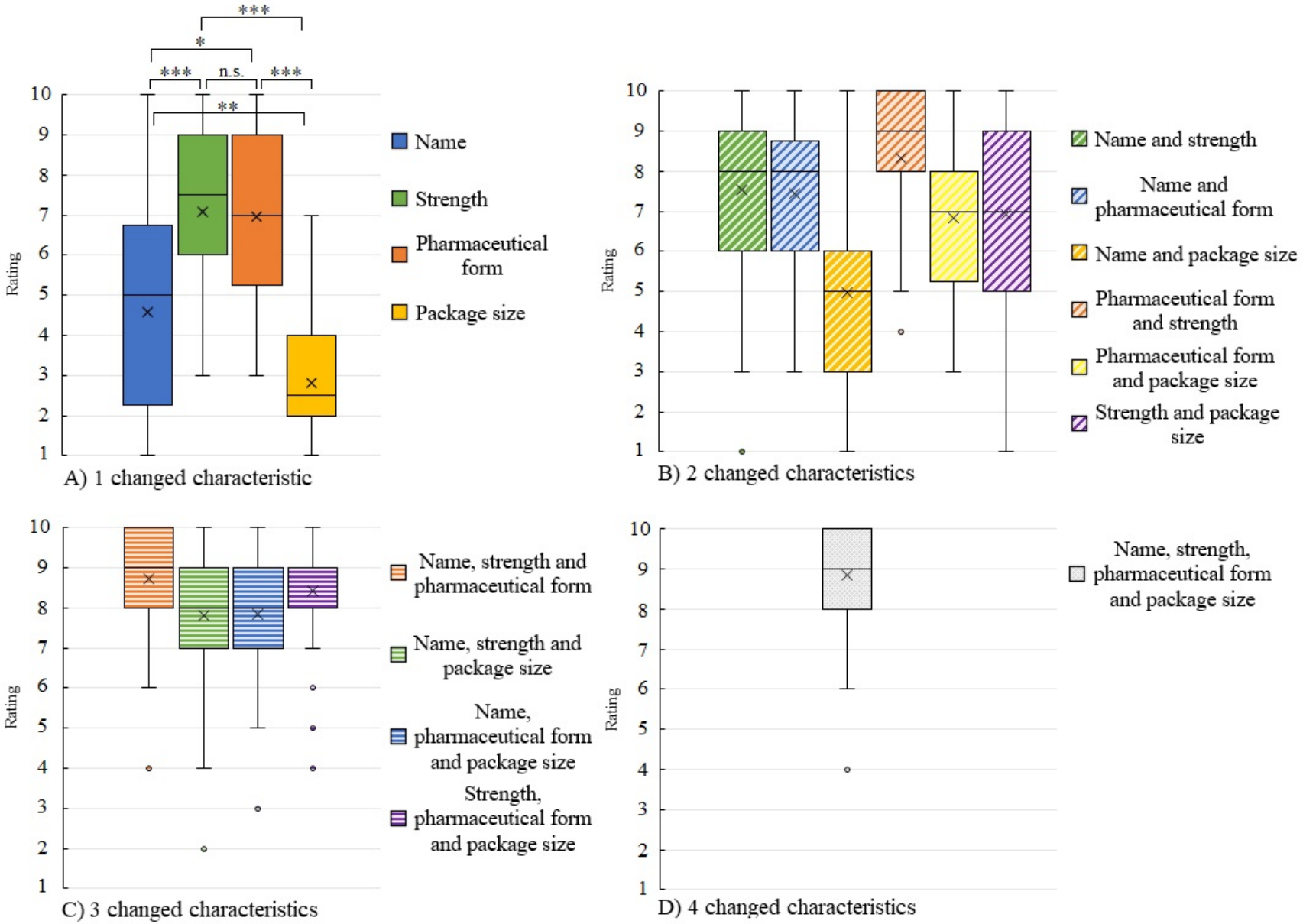
Patient group
Production
Experience
IT-systems
Storage management
Economical aspects
Categories:
Change to drug characteristics
Drug usage
Surrounding circumstances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B) 2 changed characteristics
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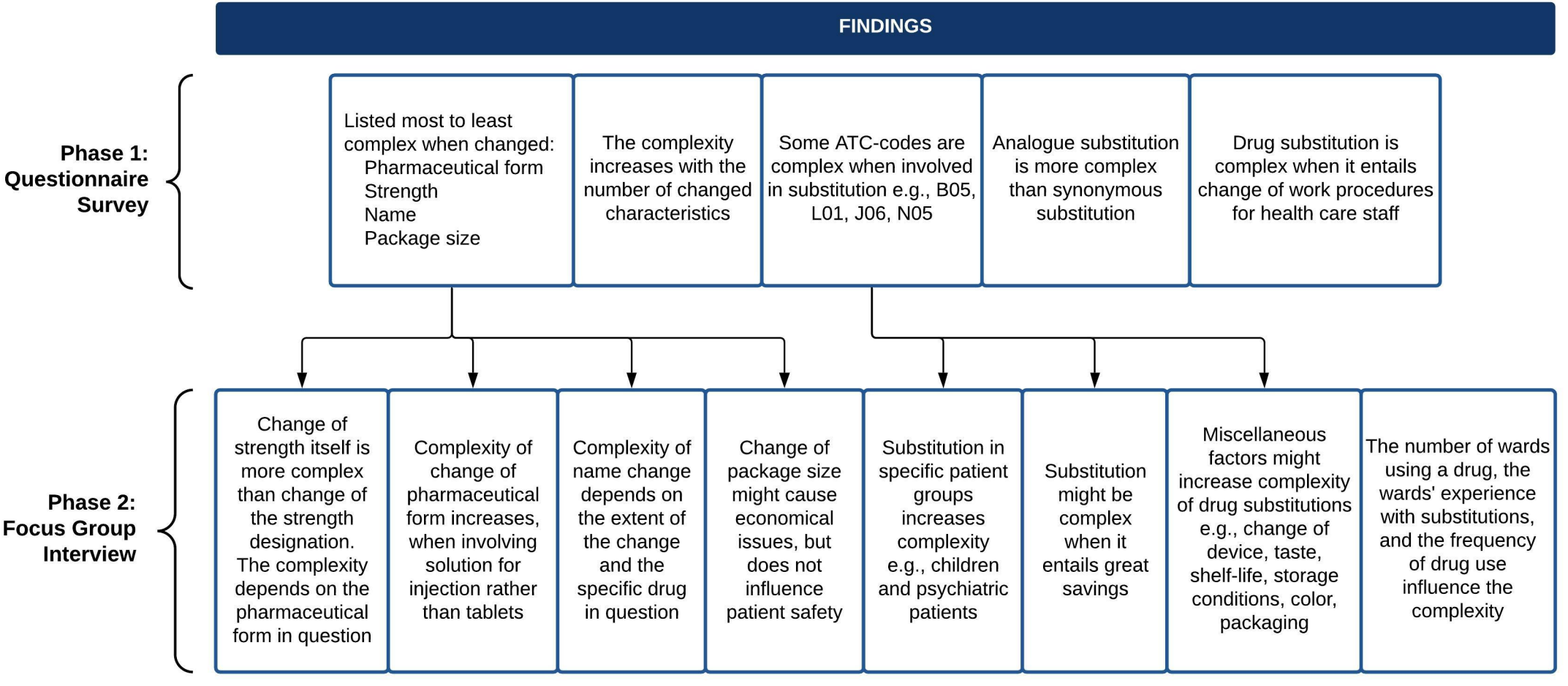
C) 3 changed characteristics
Name, strength, pharmaceutical form and package size
D) 4 changed characteristics


FINDINGS
Phase 1: Questionnaire Survey
Listed most to least complex when changed:
Pharmaceutical form
Strength
Name
Package size
The complexity increases with the number of changed characteristics
Some ATC-codes are complex when involved in substitution e.g., B05, L01, J06, N05
Analogue substitution is more complex than synonymous substitution
Drug substitution is complex when it entails change of work procedures for health care staff
Phase 2: Focus Group Interview
Change of strength itself is more complex than change of the strength designation. The complexity depends on the pharmaceutical form in question
Complexity of change of pharmaceutical form increases, when involving solution for injection rather than tablets
Complexity of name change depends on the extent of the change and the specific drug in question
Change of package size might cause economical issues, but does not influence patient safety
Substitution in specific patient groups increases complexity e.g., children and psychiatric patients
Substitution might be complex when it entails great savings
Miscellaneous factors might increase complexity of drug substitutions e.g., change of device, taste, shelf-life, storage conditions, color, packaging
The number of wards using a drug, the wards' experience with substitutions, and the frequency of drug use influence the complexity