Title: Emergency Drug Kits at the Danish Hospital Pharmacies: A Study of the Management and Challenges

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Authors: Stine Abildgaard Knudsen Student Number: 20135841

Maria Christensen Student Number: 20135749

Supervisor: Anne Estrup Olesen, MSc.Pharm, Ph.D.

External supervisor: Hanne Plet, MSc.Pharm, Ph.D.

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Preface

This master thesis was carried out at the Department of Health Science & Technology, Faculty of Medicine at Aalborg University in an external collaboration with the Hospital Pharmacy in the North Denmark Region. The thesis consists of a list of abbreviations, two theory chapters, and the main article. The first theory chapter, *Medicine for Cardiac Arrest*, describes and evaluates the current evidence for use of vasopressors and antiarrhythmics in cardiac arrest. The second theory chapter, *The Hospital Pharmacies and Their Collaboration with Amgros*, describes the functions of the hospital pharmacies in Denmark and the procurement process of pharmaceuticals through Amgros. The article, *Emergency Drug Kits at the Danish Hospital Pharmacies: A Study of the Management and Challenges*, focuses on the management of emergency drug kits at the hospital pharmacies and challenges hereof.

List of Abbreviations

AHA: American Heart Association CPR: Cardiopulmonary resuscitation EDK: Emergency drug kit ERC: European Resuscitation Council GDP: Good distribution practice GMP: Good manufacturing practice HDA: High dose adrenaline HPN: Hospital Pharmacy in the North Denmark Region MA: Meta-analysis MIMI: The Danish executive order on manufacture and import of medicinal products and intermediate products PDDM: The Danish executive order on prescriptions and dose dispensing of medicinal products PEA: Pulseless electrical activity pVT: Pulseless ventricular tachycardia ROSC: Return of spontaneous circulation RCT: Randomized controlled trial SDA: Standard dose adrenaline SR: Systematic review VF: Ventricular fibrillation

Medicine for Cardiac Arrest

The following paragraphs describe the evidence of utilizing vasopressors and antiarrhythmics during out-of-hospital/in-hospital cardiac arrest. The selected literature is based on a high level of evidence (1), and the publication dates of all systematic reviews and meta-analyses must have been within the last 10 years (2009-2018). The paragraphs are based on one randomized controlled trial, two systematic reviews, six meta-analyses, and the two current guidelines from the American Heart Association (AHA) and the European Resuscitation Council (ERC), respectively.

One of the leading causes of death in Europe is sudden cardiac arrest, which yearly affects 350.000-700.000 individuals in the European countries (2,3). Cardiac arrest is a condition characterized by loss of effective cardiac output, and it is associated with four heart rhythms known as ventricular fibrillation (VF), pulseless ventricular tachycardia (pVT), pulseless electrical activity (PEA), and asystole (4,5). First-line treatment of cardiac arrest is cardiopulmonary resuscitation (CPR), and if the heart rhythm is shockable (VF/pVT), defibrillation is also recommended as first-line treatment. Pharmacological interventions with vasopressors, antiarrhythmics, and other drugs are second-line of treatment as the evidence for their effectiveness in cardiac arrest is limited (5-7).

Vasopressors

Whether or not to continue recommending vasopressors for resuscitation have been discussed greatly the recent years. The most common vasopressors include adrenaline and vasopressin, and the former has been widely used as first-line vasopressor agent for the four heart rhythms associated with cardiac arrest. Adrenaline is an α - and β -adrenergic agonist, and its vasoconstricting abilities is due to stimulation of α -adrenergic receptors, which increases coronary and cerebral perfusion pressure during CPR (6,8). The β -adrenergic effects are not advantageous during cardiac arrest as it increases myocardial oxygen consumption, myocardial oxygen imbalance, and cerebral vasoconstriction causing cerebral ischemia and unfavorable neurological outcomes (6).

Vasopressin, also known as antidiuretic hormone, has been proposed as an alternative to adrenaline (9). It is a neurohypophysial hormone and acts as a vasoconstrictor when binding to V1 receptors in vascular smooth muscle cells, and thereby increases inotropy along with systemic and coronary vasoconstriction. Compared to adrenaline, vasopressin is associated with i.a. less impairment of cerebral blood flow, less pulmonary constriction and a longer half-life (6). Nonetheless, vasopressin is also associated with adverse effects such as increased systemic vascular resistance and myocardial afterload.

The ERC and the AHA find it reasonable to administer 1 mg of adrenaline every 3-5 minutes during CPR (5,8). This reasoning is supported by reviews, which found that this dose of adrenaline is associated with increased return of spontaneous circulation (ROSC) and survival to hospital admission compared to placebo (9,10), but whether adrenaline is superior to vasopressin is inconclusive (9,11). Additionally, high doses of adrenaline (5-15 mg) compared to the standard dose are associated with increased ROSC and survival to hospital admission especially for patients with PEA and asystole; however, it is also associated with increased neurological side effects (9,10). In contrast, the majority of the systematic reviews and meta-analyses have found no differences between adrenaline, vasopressin, and placebo during cardiac arrest in terms of survival to hospital discharge and neurological outcome (6,9-11). Whether to combine adrenaline and vasopressin or use them in succession has been tested as well, but none of these improved the long-term survival compared to the drugs administered alone (6,10,12). One the contrary, when considering the subgroup of patients with asystole, vasopressin with or without adrenaline has been associated with significantly higher rates of ROSC and long-term survival compared to adrenaline alone, especially when administered within 20 minutes (6,11,12). Table A illustrates the main study outcomes of the above-mentioned studies regarding the use of vasopressors during cardiac arrest.

Because of different study designs, objectives, ethical dilemmas, and underpowered studies limited conclusions of whether vasopressors improve the outcome of cardiac arrest can be drawn (12). In order to determine whether the use of vasopressors is beneficial or harmful, randomized, placebocontrolled, double-blinded trials conducted on larger populations are required (10).

Antiarrhythmics

Before the publication of the ALIVE trial in 2002 (13), lidocaine was recommended as the first-line antiarrhythmic agent during shock-resistant VF or pVT (6). The results from the ALIVE trial revealed that administration of amiodarone significantly increased survival to hospital admission compared to lidocaine (13). Therefore, the latest versions of the AHA and ERC guidelines recommend amiodarone as a first-line antiarrhythmic agent (5,8). However, the use of antiarrhythmics in cardiac arrest is still questionable (6). Physiologically, amiodarone controls ventricular arrhythmias by blocking cardiac potassium channels, which increases the refractory period in the myocytes and decreases the atrioventricular conduction rate, which in turn allow the ventricles to repolarize. Apart from the beneficial effects, amiodarone is also associated with common side effects such as hypotension and bradycardia in patients with ROSC (5). The ERC and AHA recommend an intravenous dose of 300 mg amiodarone after three shock attempts with the defibrillator and a further dose of 150 mg after five shocks (5,8).

Lidocaine is a second-line antiarrhythmic agent, and it blocks the cardiac sodium channels and thereby increases the refractory period in the myocytes and raises the depolarization threshold, and thus minimizing the risk of early action potentials (5,8). Toxic doses of lidocaine can result in paresthesia, confusion, and convulsions, and therefore a low dose of lidocaine, such as 100 mg, after three shock attempts followed by an additional dose of 50 mg, if necessary, are considered appropriate according to the ERC guideline (5).

Even though the ALIVE trial found amiodarone to be superior to lidocaine in regard to survival to hospital admission (13), a systematic review concludes that amiodarone and lidocaine are equivalently superior to placebo regarding survival to hospital admission (2). Nevertheless, two other reviews conclude that there is no definite evidence that the administration of any antiarrhythmic agent significantly increase the occurrence of ROSC or survival to hospital admission compared to placebo (14,15). Evidently, there is no consensus regarding the effect on short-term survival after administration of an antiarrhythmic agent. Concerning the rate of survival to hospital discharge, the review by Khan *et al.* demonstrates superiority of lidocaine over amiodarone (15). One the contrary, other reviews generally agree that there are no significant differences between administration of an antiarrhythmic agent and placebo in terms of survival to hospital discharge and neurological outcome (2,6,14). This could be due to the fact that the studies included in the reviews were underpowered, and therefore not able to detect differences in long-term survival (2,6). Table B illustrates the main study outcomes of the above-mentioned studies regarding the use of antiarrhythmics during cardiac arrest.

The inconclusive evidence for the use of antiarrhythmics in cardiac arrest illustrates the necessity for further investigations with large multicentre randomized clinical trials examining both existing and future antiarrhythmic drugs (6).

Table A: Comparison of treatment outcomes for different combinations of adrenaline, vasopressin, and placebo. The greater than sign (>) is used to indicate what drug (combination) the individual articles are supporting. A: Return of spontaneous circulation (ROSC), B: Survival to hospital admission, C: Survival to hospital discharge, and D: Neurological outcome. HDA: High dose adrenaline, MA: Meta-analysis, RCT: Randomized controlled trial, SDA: Standard dose adrenaline, and SR: Systematic review.

Study	Study design	Included studies	Types of studies (quantity)	Intervention and control	Outcomes reported	Main study outcome
Larabee et al.	SR	32	- RCT + MA of RCT (18)	- Adrenaline vs. placebo	A-D	Supporting: A
(2012) (9)			- Interventional studies (12)	- Vasopressin vs. placebo		(adrenaline > placebo)
			-Observational studies (2)	- Adrenaline vs. vasopressin		(HDA > SDA)
				- Adrenaline/vasopressin vs. adrenaline		Neutral: B-D
				- SDA vs. HDA		
Layek et al.	MA	10	- RCT (10)	- Adrenaline vs. vasopressin	A-D	Neutral: A-D
(2014) (12)				- Adrenaline/vasopressin vs. adrenaline/placebo		
				- Vasopressin after adrenaline vs. placebo		
Lin et al.	MA	14	- RCT (14)	- Adrenaline vs. placebo	A-D	Supporting: A-B
(2014) (10)				- Adrenaline vs. vasopressin		(adrenaline > placebo)
				- Adrenaline/vasopressin vs. adrenaline		(HDA > SDA)
				- SDA vs. HDA		Neutral: C-D
Lundin et al.	SR	47	- Interventional studies (25)	- Adrenaline vs. placebo	A-D	Neutral: A-D
(2016) (6)			- Observational studies (22)	- Adrenaline vs. vasopressin		
				- Adrenaline/vasopressin vs. adrenaline		
				- Adrenaline/vasopressin vs. adrenaline/placebo		
				- SDA vs. HDA		
Mentzelopoulos	MA	6	- RCT (6)	- Adrenaline vs. vasopressin	A-D	Neutral: A-D
et al. (2012)				- Adrenaline/vasopressin vs. adrenaline		
(11)				- Vasopressin after adrenaline vs. adrenaline		

Table B: Comparison of treatment outcomes for amiodarone, lidocaine, and placebo. The greater than sign (>) is used to indicate what drug (combination) the individual articles are supporting. A: Return of spontaneous circulation (ROSC), B: Survival to hospital admission, C: Survival to hospital discharge, and D: Neurological outcome. MA: Meta-analysis, RCT: Randomized controlled trial, and SR: Systematic review.

Study	Study design	Included studies	Types of studies (quantity)	Interventional and control	Outcomes reported	Main study outcome
Chowdhury et	MA	12	- RCT (4)	- Amiodarone vs. placebo	A-D	Neutral: A-D
al. (2018) (14)			- Observational studies (8)	- Lidocaine vs. placebo		
				- Amiodarone vs. lidocaine		
Dorian et al.	RCT	-	-	- Amiodarone vs. lidocaine	B-C	Supporting: B-C
(2002) (13)						(amiodarone > lidocaine)
Khan et al.	MA	7	- RCT (3)	- Amiodarone vs. placebo	A-C	Supporting: C
(2017) (15)			- Observational studies (4)	- Lidocaine vs. placebo		(Lidocaine > amiodarone)
				- Amiodarone vs. lidocaine		(Lidocaine > placebo)
						Neutral: A-B
Lundin et al.	SR	6	- RCT (2)	- Amiodarone vs. placebo	C-D	Neutral: C-D
(2016) (6)			- Observational studies (4)	- Lidocaine vs. placebo		
				- Amiodarone vs. lidocaine		
Sanfilippo et	MA	7	- RCT (3)	- Amiodarone vs. placebo	B-D	Supporting: B
al. (2016) (2)			- Observational studies (4)	- Lidocaine vs. placebo		(amiodarone > placebo)
				- Amiodarone vs. lidocaine		(lidocaine > placebo)
						Neutral: C-D

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The Hospital Pharmacies and Their Collaboration with Amgros

Medicine utilized in medical emergencies such as cardiac arrest or anaphylactic shock can be combined into emergency drug kits (EDK). The kits include all the vital medications and utensils necessary for specific emergencies and may in some situations be the difference between life and death (1,2). The hospital pharmacies in Denmark produce and distribute EDKs to the public hospitals and other customers as a service in exchange for payment (1,3). At present, eight hospital pharmacies are situated within the five regional authorities in Denmark (Fig. A), and they are funded by the state and managed by the Danish regions (4,5).

Figure A: The eight hospital pharmacies in Denmark. The white dots illustrate the locations of the hospital pharmacies in the different regions. Modified from (4,6).



Besides packing EDKs to the public hospitals, the hospital pharmacies also distribute a standard assortment of pharmaceuticals to the hospitals. Further, they manufacture hospital-specific drugs and deliver services within clinical pharmacy (7-9). Common for all the hospital pharmacies is that they procure about 99 % of the drugs utilized at the public hospitals through a pharmaceutical procurement organization called Amgros (4).

Amgros is funded by the state and managed by the Danish regions as well. By centralizing the procurement of pharmaceuticals into one company, Amgros creates economies of scale for the regions without compromising quality and patient safety. In 2016, the Danish regions saved DKK 2.8 billion due to the procurement process by Amgros and the savings increase yearly (4). Annually, Amgros invites to submit bids for the supply of drugs to the hospitals through competitive tendering.

The entire tendering process is accomplished through an online tendering system, in which the suppliers make an offer on the pharmaceuticals on call. Apart from the price of the drug, factors such as the quality, consistency, and effectiveness of the drug are also considered in the tendering process (10). The supplier, who wins the contract, must supply the hospitals for the period stated in the contract (11). The public procurements are regulated by the EU Public Procurement Directive and the Danish Public Procurement Act. Normally, procurement of goods in the EU must exceed a threshold value of DKK 1.5 million to initiate a tender round; however, to ensure competition Amgros makes EU calls for tenders for purchases exceeding a value of DKK 500,000 (12). The drugs purchased by Amgros at a discounted price are part of a supply chain involving several steps (13) (Fig B). First, the hospitals predict a demand and then order the drugs at the local hospital pharmacy. In some cases, the hospital pharmacies manufacture the drugs themselves, such as total parenteral nutrition, cytostatics, and coupled antibiotics. Otherwise, they place the orders to Amgros through ApoVision, an online system for monitoring economics, stock, and logistics (14). Subsequently, Amgros forwards the orders to the supplier or wholesaler, who delivers the drugs to the hospital pharmacies. The hospital pharmacies are in charge for distributing the drugs to the hospital wards (13).

Figure B: The drug supply chain. The supply chain illustrates the interaction between the different operators including the hospital, the hospital pharmacy, Amgros, and the supplier/wholesaler (4,13,15,16).



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Emergency Drug Kits at the Danish Hospital Pharmacies: A Study of the Management and Challenges

Stine Abildgaard Knudsen and Maria Christensen

Department of Health Science & Technology, Faculty of Medicine, Aalborg University, Denmark.

Introduction: Access to emergency drug kits (EDKs) during medical emergencies can be life-saving; however, recent doubts about the quality of the kits have been expressed. Additionally, the Hospital Pharmacy in the North Denmark Region (HPN) does not currently have an effective method to manage the Amgros-tender in relation to the EDKs even though this can be a major challenge.

Objectives: The first objective was to determine and compare the management of EDKs at the hospital pharmacies in Denmark, whereas the second objective was to ease the decision-making of whether it is worthwhile for the HPN to comply with the Amgros-tender in relation to the EDKs. **Methods**: The hospital pharmacies in Denmark were enrolled in a cross-sectional study. Information about the management and challenges of the EDKs was inquired by the means of a question-naire developed for this purpose. The responses were analyzed by thematic analysis and simple statistics, and the results were used to create a tool able to manage drug replacements in the EDKs. **Results**: All eight hospital pharmacies completed the questionnaire, and the distribution between single-use and reusable packaging is nearly equal. The hospital pharmacies comply with a variation of regulations of which good distribution practice is the most common. Six hospital pharmacies experience challenges with drug replacements in the EDKs and only one hospital pharmacy complies completely with the Amgros-tender. The majority of the hospital pharmacies use parameters such as *price of the new drug* and *potential expense for new packaging* in their decision of whether to comply with the Amgros-tender. To ease this decision, a tool able to calculate the economic outcomes of drug replacements in the EDKs was created.

Conclusion: The management of the EDKs varies greatly among the hospital pharmacies, and national requirements are therefore encouraged to ensure the quality. The challenges experienced with drug replacements reflect that complying with the Amgros-tender can be troublesome. A tool was created to ease the decision of whether it is worthwhile for the HPN to comply with the Amgrostender for the EDKs.

Introduction

A medical emergency such as cardiac arrest or anaphylactic shock can be life-threatening, and the outcome often depend on access to relevant drugs and utensils (1,2). Therefore, keeping the essential drugs and utensils in a ready-to-use kit can make the difference between life and death (3). Kits of this sort are often referred to as emergency drug kits (EDKs) and are in Denmark produced by the hospital pharmacies (4). Beyond that, the hospital pharmacies also distribute the EDKs to the public hospitals ensuring that the healthcare providers have easy access to the necessary remedies during emergencies. As quality and patient safety are of utmost importance in the healthcare system, these are ensured by standardized working procedures based on regulative requirements; however, no national requirements for the management of EDKs are declared (5,6). Therefore, the regulations the hospital pharmacies adhere to and what packaging they use etc. may be distinctly different resulting in EDKs of varying qualities. This concern is strengthened by critical deviations related to quality observed for the EDKs at the Hospital Pharmacy in the North Denmark region (HPN), indicating a need of improvement in this area. To ensure high quality of the kits across the hospital pharmacies in Denmark, national requirements standardizing the management of EDKs are needed. To achieve this, firstly it is necessary to determine and compare the management of EDKs at the hospital pharmacies in Denmark, which in the future renders it possible to develop the most effective standardized working procedures in this regard.

Most of the drugs used at the public hospitals including the drugs in the EDKs are annually subjected to a tender round, where Amgros invites to submit bids for the supply of drugs (7). Given the fact that Amgros is owned and managed by the five Danish regions (8), the hospital pharmacies are expected to buy the discounted drugs through Amgros. Buying the drugs through Amgros and always replacing them after a new tender is in this study defined as complying with the Amgros-tender. However, compliance with the Amgros-tender can be a major challenge in relation to the EDKs. Even though the Amgros-tender results in great savings for the Danish healthcare system in an overall perspective (7), replacement of the drugs in the EDKs do not always end in cost-reductions. This is due to the fact that drug replacements can be a comprehensive, timeconsuming, and expensive procedure, as it requires procurement of the new drug, potential procurement of new packaging along with additional quality assurance etc. (9). If complying with the Amgros-tender becomes too comprehensive, the hospital pharmacies must increase the prices of the EDKs, and as a result the hospitals may discontinue to purchase them. This may cause the hospitals to resort to other options than the quality assured EDKs from the hospital pharmacies, which will diminish the patient safety, and thereby minimize the chance of a positive outcome of the emergency (10,11). Due to the numerous challenges with the EDKs, the hospital pharmacies are required to decide whether it will be worthwhile to comply with the Amgros-tender for the EDKs. Nonetheless, the HPN does not currently have an effective method for this decision-making indicating an area with improvement potential.

Study Aim

The first objective of the thesis was to determine and compare the management of EDKs at the hospital pharmacies in Denmark, whereas the second objective was to ease the decisionmaking of whether it is worthwhile for the HPN to comply with the Amgros-tender for the EDKs. The first objective was accomplished by developing a questionnaire about the EDKs and analyzing the responses thereof. The second objective was accomplished by applying knowledge obtained from the questionnaire and employees at the HPN to create a tool able to facilitate the economic outcomes of drug replacements in the EDKs.

Methods

Study Design and Participants

The eight hospital pharmacies in Denmark were invited to participate in the cross-sectional study, and they were informed that participation was voluntary and non-anonymous. Emails were sent to the administrative personnel of the hospital pharmacies, who helped uncover the most qualified employees for completing the questionnaire. An email with a description of the study and the link to the online questionnaire were sent to the respective employees. Furthermore, their assortment of EDKs and the content thereof were requested. The hospital pharmacies were compensated by non-monetary means in the form of a summary of the study results after end of study.

The respondents had a deadline of nine workdays to complete the questionnaire. In case of missing responses, the hospital pharmacies were contacted after nine workdays and if necessary fourteen.

Unstructured Interviews

In order to acquire first-hand knowledge of the EDKs, unstructured interviews with employees from the HPN were carried out. The interviews were conducted with the use of thematic questions, but without a complete interview guide. The responses, documented either by hand or on a computer, were utilized without subsequent thematic analysis. The economics of the EDKs and challenges thereof were discussed with the hospital pharmacist and the production manager. The employees working in the EDK production provided the authors with an awareness of the challenges occurring in the production during drug replacements, and a quality assurance specialist explained the regulatory requirements and her role in ensuring the quality of the EDKs.

Development of Questionnaire

A quantitative and qualitative methodology was applied in the form of a questionnaire to determine the management of EDKs at the hospital pharmacies (12). The questionnaire was developed specifically for this study by the means of the knowledge from the unstructured interviews. It was developed with consideration to unambiguous and appropriate phrasing, the type of questions along with time demands of the respondents (13-15). The questionnaire consisted of two forms and contained mainly closed-ended questions in the form of multiple response, multiple choice, and yes/no questions along with a few open-ended questions. The first form contained general questions about the packaging of EDKs, customers, feedback, and the adherence to regulations (Appendix I). The second form contained questions about challenges with the EDKs in relation to the Amgros-tender and their working procedure for drug replacements in the EDKs. The questionnaire was estimated to take 15 minutes to complete, and combined, the two forms contained 13 main questions. Depending on the respondents' answers to those, they received further sub-questions. The questionnaire was developed in the online data management platform, SMART-TRIAL (Version 2.6, MEDEI ApS, Aalborg, Denmark) and a free subscription was granted.

Before the initiation of the study, the questionnaire was subjected to a pilot study conducted on five employees at the HPN (16). Based on their responses and feedback, the questionnaire was subsequently revised.

Processing of the Questionnaire

A qualitative data analysis in the form of thematic analysis was performed to analyze the responses of the open-ended questions. Coding categories were developed based on the thematic content of the responses. Subsequently, each response was labelled with one or more codes, which was used to identify patterns and themes enabling quantifiable interpretation of the responses (17,18).

A quantitative data analysis in the form of simple counts were applied for the responses

of both the closed-ended and open-ended questions (19). If the hospital pharmacies were unable to provide some of the requested information, it was considered missing and therefore not included in the analyses. The figures used to illustrate the results were created in either draw.io (Version 8.6.8, Northampton, UK) or SPSS (Version 25.0, IBM Corp., New York, USA) and modified in the image processing program, GIMP (Version 2.8.22, 2017). Only the pertinent questions from the questionnaire were included in the analyses.

Development of an Economic Calculation Tool for EDKs

To ease the decision-making of whether it is worthwhile to comply with the Amgros-tender for the EDKs, a tool was created to facilitate the economics of drug replacements in the EDKs. Knowledge from the questionnaire and the unstructured interviews was used to establish the important economic parameters of drug replacements (Fig. 1). These parameters were utilized to create functions able to calculate the economic outcomes of drug replacements (Appendix II). The functions were entered in a Microsoft Excel® spreadsheet (Version 16.0, 2016 MSO USA), in which the input-cells were subjected to data validation, whilst the rest of the cells were protected to avoid modifications. The tool was phrased in Danish and the ease of use was assessed by two employees at the HPN. The reliability of the tool was tested through test cases.

Figure 1: Economic parameters of drug replacements. The figure illustrates the parameters of the tool that the user must fill-in. They are divided into parameters related to the current drug, the new drug along with general parameters. The values of the parameters written in italics are entered in advance in the tool but can be altered if necessary. EDK: Emergency drug kit.



Results

All eight hospital pharmacies in Denmark completed the questionnaire. It was completed twice in the Central Region, since the production of EDKs is allocated to two separate pharmacy departments. The two responses from the Central Region were combined, resulting in a total of eight respondents. The majority of the responses are presented in the following sections, while the rest are accounted for in Appendix III. All results are presented as quantity of hospital pharmacies.

Packaging

All eight hospital pharmacies responded that they produce EDKs and that the assortment and contents of the kits are selected in collaboration between the hospital pharmacies, the hospitals, and specialists assigned by the Regional Drug Committees. The quantity of hospital pharmacies that produce either single-use or reusable EDKs is nearly equal (Fig. 2A). Only one hospital pharmacy produces both single-use and reusable EDKs. After usage of the single-use kits, the packaging along with the

Figure 2: EDK packaging **A**) illustrates the quantity of hospital pharmacies that package single-use EDKs, reusable EDKs or both. **B**) illustrates the distribution of single-use and reusable packaging for the different types of EDKs among the hospital pharmacies. The *Mixed EDKs* category covers EDKs that contain drugs used for multiple types of emergencies. EDK: Emergency drug kit.



Figure 3: Arguments for packaging preferences. The figure illustrates the arguments of the hospital pharmacies for packing single-use and reusable EDKs.

Single-use EDKs (n = 5)

Quality assurance (n = 3)
Less working capacity (n= 2)
Justifiable amount of waste (n =1)
Made of disposable materials (n =1)

remaining drugs are discarded, whereas the packaging and the remaining drugs are reutilized in the reusable kits.

The hospital pharmacies were asked to state why they produce single-use EDKs or reusable ones. The most common reason for using single-use EDKs was quality assurance, as the hospital pharmacies cannot ensure that reusable EDKs are managed correctly at the hospitals e.g. stored at a proper temperature (Fig. 3). It was also stated that single-use EDKs are preferable as they require less working capacity related to administration and repacking of the EDKs along with no cleaning procedures. The most common argument for reusable EDKs is that they are more resource efficient in terms of reduced discard of drugs and utensils and recycling of the packaging, which allows the hospital pharmacies to sell the EDKs at a low price

Even though the distribution of hospital pharmacies that produce single-use EDKs and reusable EDKs is nearly equal, the majority of the produced EDKs are reusable (Fig. 2B). In addition, for the individual types of EDKs, the distribution between single-use and reusable packaging is varying. For instance, the packaging for anaphylactic shock and convulsions are

Reusable EDKs (n = 4)

- Recycling of containers (n = 4)
- Reduced discard of drugs and utensils (n = 4)
 Less working capacity (n = 2)
- Cheaper sale price (n = 2)

mainly single-use, whereas the packaging for EDKs like anesthesia along with pregnancy and birth is mainly reusable. An elaboration of the EDKs are available in Appendix III.

In relation to the production of EDKs, some hospital pharmacies produce multiple EDKs for the same type of emergency. This is because some EDKs have been regionalized, whereas others are still produced for specific hospitals and wards. For example, even though two hospital pharmacies produce EDKs for convulsions (Fig. 2B), one of them produce three different kits to the hospitals within that region.

Regulatory Compliance

The hospital pharmacies stated which regulation or combination of regulations they adhere to in their management of EDKs (Fig. 4). The responses were diverse as they use between one and four regulations in five different combinations; however, good distribution practice (GDP) is the most common regulation regardless of what packaging the hospital pharmacies use. Even though the hospital pharmacies are obligated to comply with all aspects of the regulations they adhere to, employees at the HPN indicated that they only comply with some as**Figure 4:** The use of regulations with respect to packaging. The figure illustrates the combinations of regulations that are used in the management of EDKs at the hospital pharmacies coupled with the packaging they use. EDK: Emergency drug kit, GDP: Good distribution practice, GMP: Good manufacturing practice, MIMI: The Danish executive order on manufacture and import of medicinal products and intermediate products, and PDDM: The Danish executive order on prescriptions and dose dispensing of medicinal products.



pects. This might also apply to the other hospital pharmacies, and since they were not asked to specify what aspects they comply with, it is unknown whether they comply with all aspects of the selected regulations or solely some of them.

Challenges of Drug Replacements and Compliance with the Amgros-Tender

Six hospital pharmacies reported that they experience challenges with drug replacements in the EDKs, with the most common challenges being *packaging problems* and *additional labor costs* (Fig. 5). Five out of the six hospital pharmacies that experience drug replacement challenges comply conditionally with the Amgros-tender, whereas one hospital

pharmacy complies completely with the Amgros-tender, meaning that they replace the drugs in the EDKs according to the new tender. The last two hospital pharmacies do not experience any challenges in this regard. One of them complies conditionally with the Amgrostender, whilst the other does not comply at all. No compliance indicates that the drugs in the EDKs are exclusively replaced, when they are about to expire or the stock is spent. In relation to drug replacements occurring after the Amgros-tender, none of the hospital pharmacies recall the EDKs to replace the drugs before expiration of the kits. **Figure 5:** Drug replacement challenges in the EDKs. The figure illustrates the challenges (experienced by six of the hospital pharmacies) of drug replacements along with their degree of compliance with the Amgros-tender. * includes challenges with drug shortage, non-registered branded products and relocation of drugs in the EDKs each experienced by one hospital pharmacy. EDK: Emergency drug kit.



Parameters for Drug Replacements

The hospital pharmacies were asked to state which parameters they include in their decision-making regarding drug replacements in the EDKs. The six hospital pharmacies that comply conditionally with the Amgros-tender apply relevant parameters to decide whether to perform drug replacements (Fig. 6).

Figure 6: Parameters for drug replacements. The figure illustrates the most common parameters used in the decisionmaking of whether to comply with the Amgros-tender in the EDKs for the six hospital pharmacies that comply conditionally with the Amgros-tender. EDK: Emergency drug kit.



Potential expense for new packaging along with price of the new drug are the most common parameters used by six of the hospital pharmacies in their decision-making. In fact, three out of six hospital pharmacies reported that the applicability of the current packaging is a critical parameter for complying with the Amgros-tender. In addition, the majority of the hospital pharmacies also apply other relevant parameters such as price of the current drug in new Amgros-period and predicted yearly demand of the drug in their decision-making.

Economic Calculation Tool for EDKs

The Microsoft Excel-spreadsheet constitutes *the economic calculation tool for EDKs*. The tool along with instructions for use created for the HPN are available in Appendix IV and Appendix V, respectively. The tool provides the total costs of keeping the current drug and replacing the current drug with the new drug. The difference between these two costs equals the savings or additional costs for the drug replacement. The reliability of the tool was confirmed through test cases.

Appendix IV provides a real example of the total costs of a drug replacement, which was considered too expensive by the HPN to complete. The example provides the costs of replacing Solu-Medrol[®] with Depo-Medrol[®] in the EDK for anaphylactic shock. The greatest additional costs for the drug replacement are illustrated in Table 1.

 Table 1: The greatest additional costs of replacing Solu

 Medrol[®] with Depo-Medrol[®].

Additional costs

Drug price	DKK 165,450.00
Labor costs	DKK 16,050.00
Total	DKK 183,000.00

Discussion

The current study established that the management of packaging, regulatory compliance, and the Amgros-tender in relation to the EDKs vary greatly among the eight hospital pharmacies in Denmark. Furthermore, an Excel-based tool was created to ease the decision-making of whether to comply with the Amgros-tender in the EDKs.

Each hospital pharmacy selects the assortment and contents of the EDKs in collaboration with the hospitals and specialists assigned by the Regional Drug Committees. This results in variation of the EDKs across the hospitals both within and among the regions. Nevertheless, as the former Ministry of Health and Prevention stated that patients are entitled to receive the same treatments independent of location (20), the EDKs should be standardized as well. This is further supported by the fact that the Danish Medicines Council has created national treatment guidelines to ensure homogenous treatments of high quality throughout the hospitals in Denmark (21). Further, if healthcare professionals work at different hospitals with dissimilar EDKs (22), the variation within the kits may cause confusion during an emergency, and therefore potentially compromise the patient safety. Additionally, as some hospitals have specific requests for the contents of the kits, some hospital pharmacies produce multiple hospital-specific EDKs for i.a. cardiac arrest. This is a resource-demanding process compared to the production of one regionalized EDK for cardiac arrest, which is the reason the HPN strives to only produce regionalized EDKs (4,23). Based on this, establishment of a national drug committee that regularly updates national guidelines for the assortment of EDKs and their contents based on medical evidence is encouraged by the authors.

Further, these guidelines should also standardize the packaging of the kits. Currently, there is no consistency of whether the hospital pharmacies utilize single-use or reusable packaging for the different types of EDKs. Concerning the environment, reusable EDKs are a great advantage, as apart from reusing the packaging, the unused drugs can be included in the kits again (24). This renders it possible to sell the EDKs at a low price, which is highly relevant, as the hospitals have declined the EDK service in the past due to high prices. To ensure patient safety, it is critical that the hospitals utilize the quality assured EDKs from the hospital pharmacies (4). Further, the fact that the majority of the EDKs are reusable support the statement that the hospitals find them preferable. Nonetheless, the greatest advantage of single-use EDKs is that they simplify the

process of fulfilling the regulatory requirements of good manufacturing practice (GMP) or GDP (25-27). In relation to resale of reusable EDKs, it is in the GMP and GDP required that the drugs have been transported, stored, and handled in compliance with the specific requirements to ensure the quality of the returned kits. As this would be extremely extensive to ensure and document, the U.S. Food and Drug Administration along with the British Medical Association state that the quality cannot be guaranteed after the drugs have left the hospital pharmacy and must therefore not be resold (28,29). Taking these statements into account, it is evident that by using single-use packaging compared to reusable, it is easier to comply with GMP and GDP to ensure quality and thereby patient safety. This could be the reason that four hospital pharmacies choose solely to produce single-use EDKs. Interestingly, the majority of the hospital pharmacies that package reusable EDKs stated that GMP or GDP are part of the regulations that they adhere to. Nonetheless, as it is unknown which aspects of the GMP and GDP the hospital pharmacies adhere to, it is uncertain if they meet the strict requirements of these regulations related to reselling of drugs. Besides the reselling aspect, the four regulations differ in several ways of which one of the most important aspects is the quality management system. In the GMP, GDP, and the Danish executive order on manufacture and import of medicinal products and intermediate products (MIMI) it is required that self-inspections and audits are performed of the medicinal products to ensure the quality, whereas this aspect is not covered in the Danish executive order on prescriptions and dose dispensing of medicinal products (PDDM) (25-27,30,31). In relation to storage, only the GMP, GDP, and PDDM include specific requirements for parameters such as temperature, light, and humidity; however, when considering the transportation aspect, GMP and GDP are the only regulations covering this. Nevertheless, it is reasonable that the regulations do not cover the same aspects as they are created for different purposes. Still, due to their differences and the fact that the requirements of what the EDKs must fulfill is not specified anywhere, it might result in inconsistency of the quality of the kits among the hospital pharmacies. Therefore, future investigations should be aimed at examining which requirements the EDKs must fulfill in order to ensure quality and patient safety and provide the basis of a national decision.

Compliance with the Amgros-Tender

In theory, the hospital pharmacies are required to buy the drugs through Amgros, as they are both publicly owned (8). Therefore, if the hospital pharmacies do not support Amgros, it is not reasonable for the Danish state to fund the company. In practice, however, complying with the Amgros-tender in relation to the EDKs can be troublesome. This is reflected by the fact that only one of the hospital pharmacies completely with the Amgros-tender and that six hospital pharmacies experience challenges with drug replacements in the EDKs. As it is shown in the example in Economic Calculation Tool for EDKs, drug replacements in the EDKs can be an expensive procedure. From the example, it is evident that procurement of the new drug along with the labor costs were great expenses. For that reason, these parameters are frequently applied in the decision-making of whether to replace the drugs in the EDKs according to the new Amgros-tender. Even though the price per unit is cheaper for the new drug compared to the current drug, procurement of the new drug can be expensive. This is owed to the fact that the hospital pharmacies must buy an additional quantity of the new drug due to an exchange of the non-expired current drug in the expired/used EDKs. Discard of the non-expired drug is often a great expense as well, which is reflected by the fact that approximately half of the hospital pharmacies use expiry of the current drug in stock along with expiry of the current drug in the EDKs when deciding whether to comply with the Amgros-tender.

Moreover, single-use packaging allows for easier compliance with the Amgros-tender, as it is often made of cardboard, which is cheaper to purchase compared to the hard plastic packaging frequently used for reusable EDKs (32).

Given the many parameters influencing the costs of a drug replacement, determining

whether it is worthwhile to comply with the Amgros-tender can be complicated, and therefore it is relevant to assess how to facilitate the decision. The economic calculation tool for EDKs was designed with consideration to the above-mentioned parameters to facilitate this decision. In order to get maximum benefit from the tool, the hospital pharmacies must establish cut-off points determining how much is reasonable to pay for replacing drugs in the EDKs (33). The hospital pharmacist at the HPN finds an additional cost of DKK 20.000 for a drug replacement acceptable; however, it is unknown whether the other hospital pharmacies have established cut-off points. If the outcome of the tool results in additional costs beyond the cut-off point, it is reasonable to contact Amgros and explain that the price of the new drug does not provide enough savings to make the drug replacement worthwhile. This might provide incentive to find a solution satisfying for both parties. It could involve carrying out tender rounds less frequently, as this will avoid the yearly procurement of the new drugs for every EDK and decrease the labor costs. In addition, it would be beneficial for both Amgros and the supplier, who wins the contract for an extended period (34). In contrast, it must be considered whether this option reduces the competition (35), and thereby results in less savings for the Danish regions. Another important aspect is the patient safety. None of the hospital pharmacies recall the EDKs before their expiry date, and therefore the drug replacements do not occur in the beginning of the new Amgros-period for all the kits. This can result in circulation of multiple brand names among the EDKs and lack of similarity with the brand names utilized at the hospital wards, which can be problematic regarding patient safety (36). To increase the patient safety, it is preferable to recall the EDKs when implementing new Amgros-tenders, even though it would be financially demanding.

Study Strengths and Limitations

As the interviews with the employees of the HPN were not recorded, the responses were not transcribed nor analyzed by thematic analysis. This was considered a study limitation along with the fact that the interviews were performed without an interview guide (37,38).

An online questionnaire was chosen to inquire information from the hospital pharmacies as it eases the time demands of the respondents and provide the option of completing the questionnaire when convenient (39). The questionnaire was designed through the SMART-TRIAL platform to ensure a seamless user experience (40). Furthermore, as it was designed to display questions based on the previous responses, only relevant questions were presented to the respondents. Limitations of the questionnaire included the risk of the respondents misunderstanding the questions (41). Despite that the questionnaire was thoroughly evaluated by the authors and five employees at the HPN, some of the responses gave the impression that a few questions had been misunderstood. This is a common obstacle when developing a questionnaire compared to utilizing a standardized one. Further, as each hospital pharmacy was represented by one employee, it is relevant to consider that they might not have had the knowledge to answer each question satisfactory due to the diverse nature of the questions.

The economic calculation tool for EDKs covers the future costs of drug replacements, and therefore expenses such as discard of the current drug was not included in the tool. Further, as the tool was created for the purpose of this study, it has not been validated previously, which was considered a study limitation. Nevertheless, the reliability of the tool was confirmed through test cases, and the ease of use was assessed and approved by two employees at the HPN to ensure that it is suitable for the work environment at the HPN. Another consideration is that the tool was created for drug replacements occurring annually. Therefore, if the supply contract does not last exactly one year, the tool cannot be utilized as the outcome will be misleading. At last, it is relevant to mention that the tool solely provides the economic outcomes of a drug replacement and does not determine whether to perform the drug replacement. Consequently, as the tool only assists in the decision-making process, the hospital pharmacies must make the final decision themselves and consider the aspect of patient safety as well.

Conclusion

From the responses of the questionnaire developed for this study, it was evident that the management of the EDKs varies greatly among the hospital pharmacies in Denmark. This includes the packaging of the EDKs and the regulations the hospital pharmacies adhere to. Even though reusable EDKs provide great advantages, it is concluded that single-use EDKs provide the best chances of ensuring quality and patient safety. Further, in order to ensure the quality of the EDKs nationwide, national requirements specific for the EDKs are encouraged. Additionally, the majority of the hospital pharmacies experience challenges with drug replacements in the EDKs reflecting that compliance with the Amgros-tender can be troublesome. Most of the hospital pharmacies include parameters such as price of the new drug and potential expense for new packaging in their decision of whether to comply with the Amgrostender. To facilitate the decision-making process, the present study utilized these parameters to create a tool able to calculate the economic outcomes of drug replacements. As this tool provides information about the additional costs or savings, it eases the decision of whether it is worthwhile for the HPN to comply with the Amgros-tender for the EDKs.

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Appendix I - Questionnaire

The following links provide access to the online questionnaire containing the two forms. A printed version with all the main and sub-questions is available below; but as the questionnaire is constructed in such a way that the sub-questions are dependent on the responses of the main questions, the online questionnaire provides a better understanding of the principle.

Link for internal supervisor

<u>https://app.smart-</u>
 <u>trial.co/#/public/5a83de330085561654d90c99/HnBQZDlRxsiSKxYCxxTeFrZgaXiuLmuj</u>

Link for censor

<u>https://app.smart-</u>
 <u>trial.co/#/public/5a83de330085561654d90c99/ibszGct5GjvW3WnrZQUfPJVgdkyWJc98</u>

Link for external supervisor

<u>https://app.smart-</u>
 <u>trial.co/#/public/5a83de330085561654d90c99/YT9JPPo1v9ZkYzZmwQxZq8B6I7gNnUfQ</u>

Subject: Spørgeskema til	Study: Akutbakker hos de danske
appendix	sygehusapoteker
Data event: Spørgeskema	Filled out by:
Form: 1. Akutbakker	Filled out date:



Form: 1. Akutbakker

Akutbakker refererer til bakker/kasser med lægemidler og sygeplejeartikler, der anvendes i akutte situationer såsom hjertestop. Alle spørgsmålene skal besvares, før spørgeskemaet kan gemmes.

Pakker I akutbakker?
🔿 Ja
🔿 Nej
Har I tidligere pakket akutbakker?
🔘 Ja
🔿 Nej

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske sygehusapoteker	SMART-TRIAĽ
Data event: Spørgeskema Form: 1. Akutbakker	Filled out by: Filled out date:	

Hvilke akutbak	ker pakkede I?
	Akutbakker
	Ja Nej
Anafylaktisk shock	0 0
Hiertestop	Ja Nej
njeneotop	
Kramper	Ja Nej
Kamper	0 0
Doukistri	Ja Nej
FSYKIALII	0 0
	Ja Nej
Operation (anæstesi)	0 0
Akut patienttransport	Ja Nej
	0 0

Subject: Spørgeskema til	Study: Akutbakker hos de danske	
appendix	sygehusapoteker	
Data event: Spørgeskema	Filled out by:	
Form: 1. Akutbakker	Filled out date:	

Hvis I pakkede andre akutbakker, bedes I venligst angive dem

Hvorfor har I stoppet pakningen af akutbakker?

Kommenter evt. på parametre som pris, manglende efterspørgsel og manglende kapacitet på sygehusapoteket

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:	SMART-TRIAĽ
Hvem	beslutter sortimentet og indholdet af ak	utbakkerne?

Pakker I akutbakker til andre kunder end sygehusene?	
🔘 Ja	
🔘 Nej	

Hvilke andre kunder pakker I akutbakker til (f.eks. Falck og hospice)?

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:	SMART-TRIAĽ
	Pakker I akutbakker til engangsbrug?	
	🔘 Ja	
	Nej	
	\bigcirc	
Ge	nbruger I emballagen af engangs-akutbakk	erne?
	🔘 Ja	
	🔿 Nej	
	Hvilke akutbakker pakker I til engangsbrug	g?
	Anafylaktisk shock	
	Hierteston	

Hjertestop
Kramper
Psykiatri
Operation (anæstesi)
Akut patienttransport
Andre akutbakker

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske sygehusapoteker	SMART-TRIAL
Data event: Spørgeskema	Filled out by:	
Form: 1. Akutbakker	Filled out date:	

Hvilke andre akutbakker pakker I til engangsbrug?

Hvorfor har I valgt at pakke akutbakker til engangsbrug?

Kommenter evt. på parametre som patientsikkerhed, forbrug af indhold i bakken, kvalitetssikring og ønske fra kunde

Pakker I akutbakker til flergangsbrug?	
🔘 Ja	
🔘 Nej	

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:	SMART-TRIAL
	Hvilke akutbakker pakker I til flergangsbrug	?
	Anafylaktisk shock	
	Hjertestop	
	Kramper	
	Psykiatri	
	Operation (anæstesi)	
	Akut patienttransport	

Andre akutbakker

Hvilke andre akutbakker pakker I til flergangsbrug?

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:	SMART-TRIAĽ
Hvor	for har I valgt at pakke akutbakker til flergan	igsbrug?
Kommenter evt. på para	metre som patientsikkerhed, akutbakkepris, kvalitetssikring, ønske fra kunde	forbrug af indhold i bakken,
Har I mod	taget tilbagemeldinger fra kunderne vedr. al	kutbakkerne?
	🔘 Ja	
	🔘 Nej	

Subject: Spørgeskema til
appendix
Data event: Spørgeskema
Form: 1. Akutbakker



Hvad fik I tilbagemeldinger om?
Tydelige etiketter på akutbakkerne
Problemer med etiketter på akutbakkerne
Ønske om flere etiketter på akutbakkerne
Overskuelig placering af lægemidler i akutbakkerne
Uoverskuelig placering af lægemidler i akutbakkerne
Risiko for forveksling af lægemidler
Andet
Hvilke andre parametre fik I tilbagemeldinger om?

.....

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:
Hvilke retningslinjer/	bekendtgørelser følger I ift. pakning og håndtering af akutbakker?
Good manufact	uring practice (GMP)
Good distributio	on practice (GDP)
Bekendtgørelse	om recepter og dosisdispensering af lægemidler
Bekendtgørelse	om fremstilling og indførsel af lægemidler og mellemprodukter
Andre retningsl	injer/bekendtgørelser
Afkryds gerne flere	e felter, hvis I arbejder efter en kombination af flere retningslinjer

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 1. Akutbakker	Study: Akutbakker hos de danske sygehusapoteker Filled out by: Filled out date:	SMART-TRIAL
	Har I nogle kommentarer eller tilføjelser?	

Venligst angiv e-mailadresse og telefonnummer på en kontaktperson, således vi har mulighed for at stille afklarende spørgsmål

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske	
Data event: Spørgeskema	sygehusapoteker	
Form: 2. Håndtering af Amgros-	Filled out by:	
udbud i akutbakkerne	Filled out date:	

Form: 2. Håndtering af Amgros-udbud i akutbakkerne

Dette spørgeskema skal kun besvares, hvis I pakker akutbakker. *Akutbakker* refererer til bakker/kasser med lægemidler og sygeplejeartikler, der anvendes i akutte situationer såsom hjertestop. Alle spørgsmålene skal besvares, før spørgeskemaet kan gemmes.

Oplever I udfordringer ved implementering af nye Amgros-udbud i akutbakkerne?
🔿 Ja
🔘 Nej
Hvilke udfordringer oplever I?
Pladsmangel i akutbakkerne
Nyt lægemiddel passer ikke i skumindlæg
Kassation af nuværende lægemiddel
Merarbejdsomkostninger ved lægemiddelskift
Andre
Nuværende lægemiddel: Lægemiddel i akutbakkerne nu. Nyt lægemiddel: Lægemiddel, som har vundet udbuddet for ny Amgros-periode.

SMART-TRIAL

Subject: Spørgeskema til appendix Data event: Spørgeskema	Study: Akutbakker hos de danske sygehusapoteker	
Form: 2. Håndtering af Amgros-	Filled out by:	
udbud i akutbakkerne	Filled out date:	

Hvilke andre udfordringer oplever I?

Har I en arbejdsgang/instruktion for håndtering af nye Amgros-udbud ift. akutbakkerne?
🔘 Ja
🔘 Nej

Subject: Spørgeskema til appendix Data event: Spørgeskema Form: 2. Håndtering af Amgrosudbud i akutbakkerne



Hvilke parametre indgår i jeres arbejdsgang/instruktion for håndtering af nye Amgros-udbud?				
Pris for nuværende lægemiddel i ny Amgros-periode				
Lagerstatus for nuværende lægemiddel				
Udløb for nuværende lægemiddel på lager				
Udløb for nuværende lægemiddel i akutbakkerne				
Pris for nyt lægemiddel				
Arbejdstid for opdatering af nye arbejdssedler				
Antal potentielle lægemiddelskift i den specifikke akutbakke				
Potentiel udskiftning af emballage (inkl. skumindlæg m.m.)				
Forventet lægemiddelforbrug i ny Amgros-periode				
Antal af den specifikke akutbakke i omløb				
Arlig ompakningsfrekvens af den specifikke akutbakke (ift. udløb)				
Andre parametre				
Nuværende lægemiddel: Lægemiddel i akutbakkerne nu. Nyt lægemiddel: Lægemiddel, som har				

vundet udbuddet for ny Amgros-periode

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske
Data event: Spørgeskema	sygehusapoteker
Form: 2. Håndtering af Amgros-	Filled out by:
udbud i akutbakkerne	Filled out date:



Hvilke andre parametre indgår i jeres arbejdsgang/instruktion?

Subject: Spørgeskema til appendix
Data event: Spørgeskema
Form: 2. Håndtering af Amgros-
udbud i akutbakkerne



Hvilke parametre indgår i jeres overvejelser om implementering af nye Amgros-udbud?
Pris for nuværende lægemiddel i ny Amgros-periode
Lagerstatus for nuværende lægemiddel
Udløb for nuværende lægemiddel på lager
Udløb for nuværende lægemiddel i akutbakkerne
Pris for nyt lægemiddel
Arbejdstid for opdatering af nye arbejdssedler
Antal potentielle lægemiddelskift i den specifikke akutbakke
Potentiel udskiftning af emballage (inkl. skumindlæg m.m.)
Forventet lægemiddelforbrug i ny Amgros-periode
Antal af den specifikke akutbakke i omløb
Arlig ompakningsfrekvens af den specifikke akutbakke (ift. udløb) Å
Andre parametre
Nuwaranda lagamiddal: Lagamiddal i akuthakkarna nu. Nut lagamiddal: Lagamiddal aam har

Nuværende lægemiddel: Lægemiddel i akutbakkerne nu. Nyt lægemiddel: Lægemiddel, som har vundet udbuddet for ny Amgros-periode

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske	
Data event: Spørgeskema	sygehusapoteker	
Form: 2. Håndtering af Amgros-	Filled out by:	
udbud i akutbakkerne	Filled out date:	

Hvilke andre parametre indgår i jeres overvejelser?

Hvis I har noteret hvilke overvejelser, I gør jer ved håndtering af nye Amgros-udbud i akutbakkerne, bedes I venligst opsummere disse

SMART-TRIAL

Subject: Spørgeskema til appendixStudy: Akutbakker hos dData event: SpørgeskemasygehusapotekerForm: 2. Håndtering af Amgros- udbud i akutbakkerneFilled out by:Filled out date:Filled out date:		SMART-TRIAL
Tilbagekalder I de akutbakke	er, der er i omløb, når I implementere	r nye Amgros-udbud?
🔘 Ja, al	tid	

O Ja, hvis omkostningerne er tilstrækkelig lave

🔘 Nej

Tydeliggør I lægemiddelskift i akutbakkerne for kunden?

\bigcirc	Ja
0	Nej

Hvordan tydeliggør I lægemiddelskift i akutbakkerne?

Subject: Spørgeskema til appendix	Study: Akutbakker hos de danske	
Data event: Spørgeskema	sygehusapoteker	
Form: 2. Håndtering af Amgros-	Filled out by:	
udbud i akutbakkerne	Filled out date:	



Har I nogle kommentarer eller tilføjelser?

Venligst angiv e-mailadresse og telefonnummer på en kontaktperson, således vi har mulighed for at stille afklarende spørgsmål

Appendix II - Calculations Included in the Tool

The appendix illustrates the functions used to create the economic calculation tool for EDKs.

Functions

The statistical functions *MIN* and *MAX* are used to create the calculations.

The syntax of the MIN function is MIN(number 1, [number 2],...), and it returns the smallest value from the numbers provided.

The syntax of the MAX function is MAX(number 1, [number 2],...), and it returns the largest value from the numbers provided.

Current drug

Drug costs

Total drug costs = MAX((predicted yearly demand – stock status) \cdot price of the drug in new Amgros period, 0)

Labor costs

New worksheets = <u>EDKs in circulation</u> <u>columns to document refilling on worksheet</u>

Work hours for transfer of data to worksheets = $\frac{\text{new worksheets} \cdot \text{minutes for transfer of data to worksheet}}{60}$

Labor costs for transfer of data to worksheets = work hours for transfer of data to worksheets \cdot hourly wage

Total costs

Price of keeping the current drug = total drug costs + labor costs for transfer of data to worksheets

New drug

Drug costs

Extra consumption due to refilling of EDK = MIN $\left(\frac{\text{EDKs incirculation}}{\frac{(\text{shelf life of the EDK after refilling})}{12}}, 0\right)$. Components of the drug in the EDK

Total drug costs = (predicted yearly demand + extra consumption due to refilling of EDK) \cdot price of the drug

Labor costs

New worksheets = MIN
$$\left(\frac{\text{EDKs in circulation}}{\left(\frac{\text{shelf life of the EDK after refilling}}{12}\right)}$$
, EDKs in circulation

Work hours for transfer of data to worksheets = $\frac{\text{new worksheets} \cdot \text{minutes for transfer of data to worksheet}}{60}$

Labor costs for transfer of data to worksheets = work hours for transfer of data to worksheets \cdot hourly wage

Total costs

Price of replacing the current drug with the new drug

= total drug costs + labor costs for transfer of data to worksheets + total price for new packaging + basic costs

Additional costs or savings for replacing the current drug with the new drug

Additional costs or savings = price of replacing the current drug with new new drug – price of keeping the current drug

If the outcome is negative, replacing the current drug with the new drug results in savings for the hospital pharmacy. If the outcome is positive, replacing the current drug with the new drug results in additional costs for the hospital pharmacy.

When using the tool, savings are not represented by a negative outcome. Instead the tool provides information of whether the outcome is a saving or an additional cost.

Appendix III - Additional Results

This appendix provides the results of the questionnaire not included in the article. They concern the customers of the hospital pharmacies, the feedback the hospital pharmacies have received along with information about how the hospital pharmacies notify the hospitals about drug replacements in the EDKs. Furthermore, the assortment and different types of EDKs are elaborated.

Customers

The main customers of the hospital pharmacies are the local hospitals. Beyond that, three of the hospital pharmacies responded that they deliver EDKs to other customers composed of emergency medical services (Falck), local homecare services, private pharmacies, and Greenland. The packaging of EDKs to the other customers is mainly single-use except for those to the emergency medical services, which are reusable.

Feedback

Five hospital pharmacies have received feedback from their customers related to the EDKs. Three of them reported feedback related to one of the following: problems with labels, disorganized arrangement of drugs, and risks of confusion between the drugs in the kits. The additional two hospital pharmacies reported that the feedback involved requests for revision of the content along with a longer shelf life of the kits.

Notifications about Drug Replacements

Seven of the hospital pharmacies provide their customers with additional information during drug replacements in the EDKs. The information provided from the different hospital pharmacies includes a combination of informing the hospital wards prior to the drug replacement and attaching additional instructions in the kits along with extra labelling. One of the hospital pharmacies pointed out that if the change is to another brand name, it is not always relevant to provide additional information.

The assortment of EDKs

In total, the entire assortment of EDKs produced at the hospital pharmacies includes 58 kits. Fig. 1 illustrates the total number of produced kits within each category (and not the quantity of hospital pharmacies that produce them).

Figure 1: The assortment of EDKs. The figure illustrates the distribution of single-use and reusable packaging for the different types of EDKs. The *Mixed EDKs* category illustrates the quantity of EDKs that contain drugs used for multiple types of emergencies. EDK: Emergency drug kit.



The EDKs for cardiac arrest are generally similar; however, one of the hospital pharmacies produces three different EDKs for cardiac arrest termed regular, diverse, and supplement medicine for cardiac emergencies. Drugs utilized for anaphylactic shock, allergic reactions, and anaphylaxis are included in the EDKs for anaphylactic shock, whereas the EDKs for convulsions contain drugs utilized to treat seizures such as epileptic convulsions, epileptic state, or fever cramps. The EDKs used for emergencies during patient transportation include drugs for different emergencies such as cardiac arrest, convulsions, anaphylactic shock, and drug overdoses. Drugs of vital importance during anesthetic procedures are included in the EDKs for anesthesia. These drugs can prevent or treat anaphylactic shock, cardiac arrest, or malignant hyperthermia, which are potential serious complications to the anesthetics. Kits used for preeclampsia, eclampsia, postpartum bleeding, and home birth are covered by the EDKs for pregnancy and birth, whereas emergencies such as cardiac arrest and anaphylactic shock occurring in neonates and children are included in the EDKs for neonates and children. The kits that each include drugs for several emergencies are covered by the mixed EDKs, whereas kits that simply contain utensils or magnesium sulphate along with kits utilized during intubation are included in the other category.

Appendix IV - The Economic Calculation Tool for EDKs

The following link provides access to *the economic calculation tool for EDKs* along with an example of replacing Solu-Medrol[®] with Depo-Medrol[®].

https://www.dropbox.com/sh/ji9pemq3mmq04fx/AAAtOa-GlqvchZWoWhiJw84Ga?dl=0

A screenshot of the tool filled-in with the example is shown in Fig. 1 on the next page. The example illustrates the values of all the parameters along with the economic outcomes of replacing Solu-Medrol[®] with Depo-Medrol[®] in the EDK for anaphylactic shock during the Amgros-tender in 2016. The drug replacement was considered too expensive to complete at the Hospital Pharmacy in the North Denmark Region.

Figure 1: Economic outcomes of replacing Solu-Medrol[®] with Depo-Medrol[®].

1 Bereaning for skift af ét lægemiddel	
2 Udfyld nedenstående felter <u>NUVÆRENDE LÆGEMIDDEL</u> <u>RESULTAT FOR SKIFT A</u>	F ET LÆGEMIDDEL
3 Akutbakkenummer (Vnr.) 802692 Total lægemiddelpris (kr.) Totalomkostning for a	t beholde nuværende lægemiddel
4 7.170,00 kr.	15.195,00 kr.
5 Nuværende lægemiddel Nye arbejdssedler (stk.)	
6 Handelsnavn Solu-Medrol 100 Totalomkostning for a	t skifte til nyt lægemiddel
7 Pris i ny Amgros-periode (kr./stk.) 478 Arbejdstid for overførsel til nye arbejdssedler (t.)	198.195,00 kr.
8 Lagerstatus (stk.) 15 25	
9 Lønomkostning ved at	t skifte til nyt lægemiddel
10 Nyt lægemiddel 8.025,00 kr.	183.000,00 kr.
11 Handelsnavn Depo-Medrol Totalomkostninger for at behold (kr.)	
12 Pris (kr./stk.) 274 15.195,00 kr.	
13 Totalpris for ny emballage (kr.) 0	
14 Grundomkostninger (kr.) 1500 <u>NYT LÆGEMIDDEL</u>	
15 Ekstra forbrug pga. genopfyldning (stk.)	
16 Almene faktorer 600	
17 Forventet årligt forbrug (stk.) 30 Total lægemiddelpris (kr.)	
18 Akutbakker i omløb (stk.) 300 172.620,00 kr.	
19 Holdbarhed af akutbakken efter genopfyldning (mdr.) 6 Nye arbejdssedler (stk.)	
20 Enheder af lægemidlet i akutbakken (stk.) 2 300	
21 Kolonner på arbejdsseddel (stk.) 3 Arbejdstid for overførsel til nye arbejdssedler (t.)	
22 Arbejdstid for overførsel til arbejdsseddel (min.) 15 75	
23 Timeløn (kr.) 321 Lønomkostninger (kr.)	
24 24.075,00 kr.	
25 Totalomkostninger for at skifte (kr.)	
26 198.195,00 kr.	
27	
28 DIFFERENCE (NYT LÆGEMIDDEL-NUVÆRENDE LÆGEMIDDEL)	
29	
30 Lægemiddelpris (kr.)	
31 165.450,00 kr.	
32 Lønomkostninger (kr.)	
33 16.050,00 kr.	
34 Besparelse/meromkostning ved at skifte (kr.)	
35 183.000,00 kr.	

Appendix V - Vejledning til brug af Excel-værktøjet

Dette værktøj er lavet til internt brug på Sygehusapoteket Region Nordjylland.

Excel-værktøjet bør anvendes som et redskab til at beregne de økonomiske omkostninger (baseret på 1 års forbrug) for implementering af nye Amgros-udbud i akutbakkerne. Ved at indtaste værdierne for parametrene udregnes de økonomiske udfald for at beholde det nuværende lægemiddel^{*} og at udskifte til det nye lægemiddel^{**}, som har vundet Amgrosudbuddet. Samtlige felter på nær *totalpris for ny emballage* skal udfyldes før priserne kan beregnes.

En betingelse for at anvende værktøjet er, at det nuværende lægemiddel *ikke* udgår i den nye Amgros-periode. Hvis der indgår flere potentielle lægemiddelskift i *samme type* akutbakke udfyldes et Excel-ark for hvert lægemiddel. For at få den totale meromkostning/besparelse for at udskifte samtlige lægemidler i akutbakken gøres flg.: Hvis værdien i celle E10 for det ene lægemiddel er en meromkostning, lægges denne sammen med værdien i celle D18 for de andre lægemidler. Derimod, hvis værdien i celle E10 for det ene lægemiddel er en besparelse, trækkes værdien i celle D18 for de andre lægemidler fra værdien i celle E10. Mellemregningerne er tilgængelige i kolonne D, som kan vises ved at højreklikke på kolonnen og trykke på *Vis*. Værktøjet er skrivebeskyttet for at minimere risikoen for fejl, men kan låses op via flg. kode: 859478

* Nuværende lægemiddel kendetegner det præparat som allerede indgår i akutbakken.
** Nyt lægemiddel kendetegner det synonympræparat, som er billigst i den nye Amgrosperiode.

Nuværende lægemiddel

Felterne B6-B8 i Excel-arket udfyldes med værdierne for de angivne parametre for det nuværende lægemiddel. Parametrene er som følger:

- Handelsnavn
- *Pris i ny Amgros-periode (kr./stk.)*: Prisen pr. enhed (enkeltstyks).
- Lagerstatus (stk.): Mængden af lægemidlet på lager som kan holde sig i min. 1 år.

Nyt lægemiddel

Felterne B11-B14 i Excel-arket udfyldes med værdierne for de angivne parametre for det nye lægemiddel. Parametrene er som følger:

- Handelsnavn
- *Pris (kr./stk.)*: Prisen pr. enhed (enkeltstyks).
- Totalpris for ny emballage (kr.): Denne parameter inkluderer bl.a. nye skumindlæg.
 OBS: Udfyld kun hvis der er behov for indkøb af ny emballage. Totalprisen kan evt. beregnes på flg. måde:

Totalpris = pris for emballage pr. akutbakke x (antal akutbakker i omløb og på lager + 10 % ekstra)

Grundomkostninger (kr.): Dækker standardudgifter som f.eks. opdatering og kvalitetssikring af etiketter og arbejdssedler samt print heraf. Denne parameter er skønnet til 1500 kr. NB: For hvert ekstra lægemiddelskift i akutbakken bør tillægges 10 % af denne omkostning.

Almene faktorer

Felterne B17-B23 i Excel-arket udfyldes med værdierne for de angivne parametre, som gør sig gældende for både det nuværende- og nye lægemiddel. Parametrene er som følger:

- *Forventet årligt forbrug (stk.)*: Det totale forbrug baseret på konsumption og forbrug af lægemidlet grundet udløb af lægemidlet i den nye Amgros-periode.
- *Akutbakker i omløb (stk.)*: Antallet af den specifikke type akutbakke (akutbakke med samme vnr.) som er i omløb.
- *Holdbarhed af akutbakken efter genopfyldning (mdr.)*: Hvor mange måneder akutbakken kan holde sig efter genopfyldning baseret på bakkens udløbsdato.
- *Enheder af lægemidlet i akutbakken (stk.)*: Hvor mange enheder af lægemidlet der indgår i hver enkelt akutbakke.
- Kolonner på arbejdsseddel (stk.): Det totale antal kolonner på arbejdssedlen der bruges til at dokumentere genopfyldning af akutbakken. Denne parameter er sat til 3.
- Arbejdstid for overførsel til arbejdsseddel (min.): Arbejdstid afsat til at en medarbejder kan overføre batchnumre og lign. for lægemidlerne i akutbakken til en ny arbejdsseddel. Denne parameter er sat til 15 min.
- *Timeløn (kr.)*: Timelønnen for at pakke akutbakker. Denne parameter er sat til 321 kr.
 og er baseret på lønnen for en farmakonom/laborant.

Værktøjets funktion og begrænsninger

Dette værktøj inkluderer omkostninger i form af indkøb af lægemidler og emballage, print af etiketter og arbejdssedler samt løn for opdatering og kvalitetssikring af etiketter og arbejdssedler. Der indgår også løn for overførsel af information af lægemidlerne til nye arbejdssedler ved implementering af nyt Amgros-udbud i akutbakkerne. Værktøjet er baseret på, at én Amgros-periode varer 1 år, hvilket vil sige at de økonomiske omkostninger beregnes for ét års forbrug af lægemidlet. Omkostningerne for kassering af det nuværende lægemiddel ifm. lægemiddelskift er ikke inkluderet. Derudover angiver værktøjet ikke, om man skal udføre et lægemiddelskift eller ej. Det angiver kun det økonomiske grundlag for at tage en faglig vurdering.

Illustration af værktøjet

På næste side ses et screenshot af værktøjet med et eksempel på et potentielt lægemiddelskift fra Amgros-udbuddet i 2016. Eksemplet viser de økonomiske omkostninger ved at udskifte Solu-Medrol[®] med Depo-Medrol[®] i anafylaktisk shock-bakkerne (Vnr. 802692).

Decempring for skrift af et lagemiddel Utyle metanationed siles NUVERENCE LEGEMIDDEL ESULTAT FOR SNFT AF ET LEGEMIDDEL 3 Autobakknummer (Vnr.) 80269 Total lagemiddelpris (kr.) Totalomkostning for at skrifte til nytagemiddel 5 Vurernde tagemiddel (kr.sk) 80269 Total lagemiddelpris (kr.) Totalomkostning for at skrifte til nytagemiddel 6 Vurernde tagemiddel (kr.sk) 80-440 Nuvernde tagemiddel 15.195.00 kr. 7 Pin y Angros-periode (kr.sk) 80-440 Arbeigdati for overførsal til nyt arbeigdsseller (t.) Meromkostning ord at skrifte til nyt lagemiddel 1 Indestnavn Depo-Medrol Totalomkostninger for at behold (kr.) Meromkostning ved at skrifte til nyt lagemiddel 1 Handestnavn Depo-Medrol Totalomkostninger for at behold (kr.) Meromkostning ved at skrifte til nyt lagemiddel 1 Hondestnavner (kr.) Depo-Medrol Totalomkostninger for at behold (kr.) Meromkostning ved at skrifte til nyt lagemiddel 1 Vedamkostninger (kr.) Totalomkostninger for at behold (kr.) Meromkostning ved at skrifte til nyt lagemiddel 1 Profersh king forbug (sk). Opooodde kr. Numerek kr.) <td< th=""><th></th><th>A</th><th>В</th><th>С</th><th>D</th><th>E</th></td<>		A	В	С	D	E
2 Untrafference Untrafference ESULTAT FOR SURT AFT LECEMPIDEL 4 Autobas Mammer (hr.) BISUMA FOR SURT AFT LECEMPIDEL TELEMINICATION SURT AFT LECEMPIDEL 4 Image and Surt After and Surt	1	Beregning for skift af ét lægemiddel				
Number (Vn.) Note (Note (Note)) Control (Note (Note)) Control (Note) Vertande (note) <td>2</td> <td></td> <td>Udfyld nedenstående felter</td> <td></td> <td>NUVÆRENDE LÆGEMIDDEL</td> <td>RESULTAT FOR SKIFT AF ET LÆGEMIDDEL</td>	2		Udfyld nedenstående felter		NUVÆRENDE LÆGEMIDDEL	RESULTAT FOR SKIFT AF ET LÆGEMIDDEL
4 Image and the service of	3	Akutbakkenummer (Vnr.)	802692		Total lægemiddelpris (kr.)	Totalomkostning for at beholde nuværende lægemiddel
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6 Hardedmann Solu-Medral Solu-Medra Solu-Medral So	5	Nuværende lægemiddel			Nye arbejdssedler (stk.)	
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9 Imagemide Imagem	8	Lagerstatus (stk.)	15		25	
10 Nyi tagemiddei Badolanavi	9				Lønomkostninger (kr.)	Meromkostning ved at skifte til nyt lægemiddel
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