Meds Safe to combat drug waste: a feasibility and micro-costing study

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Samenvatting

Orale kankermedicijnen zijn duur en worden vaak verspild, waardoor hoge gezondheidszorgkosten en schade aan het milieu ontstaan. Een medicijnkluis, genaamd Meds Safe, is ontwikkeld om de kwaliteit van medicijnen te garanderen, waardoor ongebruikte medicijnen aan andere patiënten kunnen worden heruitgegeven. Echter, doordat het apparaat nieuw is, is er nog weinig bekend over de haalbaarheid en welke medicijnen geschikt zijn voor kostenvoordelige heruitgifte via de Meds Safe. Om dit te evalueren zijn een haalbaarheidsonderzoek en kostenanalyse uitgevoerd in twee Nederlandse poliklinische apotheken. Vragenlijsten en interviews zijn afgenomen met patiënten en apotheekpersoneel om de haalbaarheid te onderzoeken. Daarnaast is een overzicht van de processtappen voor het uitgeven en retourneren van de Meds Safe in de apotheek gemaakt om de bijbehorende kosten uit te rekenen. Vervolgens zijn orale kankermedicijnen, die voldoen aan de minimale prijs voor kostenvoordelige heruitgifte en de eigenschappen van het apparaat, geselecteerd van een lijst met eerste uitgiften.

Uit het onderzoek is gebleken dat de 15 deelnemende patiënten en vier apotheekmedewerkers de Meds Safe gemakkelijk te gebruiken vonden en denken dat het apparaat kan bijdragen aan het verminderen van medicijnverspilling. Echter, vonden ze het apparaat niet gebruiksvriendelijk. De kosten voor het gebruiken van het apparaat varieerden tussen €154 en €94. Op basis van de minimale prijs voor kostenvoordelige heruitgifte en de praktische eigenschappen van het apparaat zijn zes orale kankermedicijnen geschikt bevonden.

Uiteindelijk kan worden geconcludeerd dat de Meds Safe nog niet acceptabel is om de zes geïdentificeerde orale kankermedicijnen kostenvoordelig her uit te geven in de apotheek.

Abstract

Background: Oral anticancer drugs are frequently wasted, causing high healthcare costs and environmental pollution. A medicine locker, called Meds Safe, has been developed to guarantee drugs' quality, so unused drugs can be redispensed to other patients in need. However, because the device is a new invention, little is known about it. Therefore, the aim of this study was to evaluate the feasibility of the Meds Safe and asses operational costs to identify eligible oral anticancer drugs for cost-beneficial redispensing with the Meds Safe.

Methods: A feasibility- and micro-costing study were performed in two Dutch outpatient pharmacies. Questionnaires and interviews with patients and pharmacy employees were completed to examine the feasibility of the Meds Safe. In addition, a detailed overview of the process steps for dispensing and returning the Meds Safe in the pharmacy was made, followed by a quantification of the associated costs. Subsequently, eligible oral anticancer drugs, which met the price level for cost-beneficial redispensing and comply with the properties of the device, were identified from a list of first filling prescriptions.

Results: Fifteen patients and four pharmacy employees participated in the study. They found the Meds Safe easy to use and suitable to combat drug waste, but not user-friendly. Costs for using the Meds Safe in the pharmacy varied between €154 and €94 and four practical criteria were used for the identification. Based on the price level for cost-beneficial redispensing and the properties of the device, six oral anticancer drugs have been found eligible.

Conclusions: The Meds Safe is not acceptable to cost-beneficially redispense the identified oral anticancer drugs in the pharmacy.

Introduction

In the last couple of years, the price of oral anticancer drugs has increased considerably[1-3], with the result that the expenditures on anticancer drugs amounted €32 billion in Europe in 2018.[4] Nevertheless, around one-third of the patients using oral anticancer drugs discontinue their therapy early, due to lack of efficacy, adverse reactions or other reasons.[5-7] The impact on the healthcare budget through unused oral anticancer drugs is significant, as

the quantity and economic value of these medicines is high.[8] In addition, unused oral anticancer drugs lead to environmental damage due to drug residues being discarded or thrown down the drain,[9] causing polluted groundwater[10] and detrimental consequences for aquatic organisms.[11-13]

To counteract the consequences of medication waste, multiple adjustments in different stages of the pharmaceutical chain are necessary[14], such as a shorter prescription duration[15] or adjusting the packing size of oral medication.[16, 17] Another potential strategy to reduce medication waste is the redispensing of unused drugs.[18, 19] Good quality medicines, that remained unused by patients and are returned to the pharmacy, could then be redispensed to another patient in need.[20, 21] In most countries, however, it is juridical not allowed to redispense leftover medication due to legal restrictions or absence of clinical guidelines.[22-24] Nevertheless, several studies have shown that medication redispensing is a promising way to reduce medication waste and healthcare costs[25, 26], especially when implementing the redispensing process for high-priced drugs[27], such as oral anticancer drugs.[21] Redispensing programs in Greece[28] and the United Stated[29] have also been showing that redispensing is a way to prevent drug waste. In addition, patients[30, 31] and stakeholders[19] are willing to redispense medication, as long as the quality of these drugs can be guaranteed.

To enable redispensing unused oral anticancer drugs, a controlled process to ensure the quality of unused medication, is necessary. To meet this quality requirement, a medicine locker, called Meds Safe, has been developed. In this device, tablets and capsules can be stored at a controlled temperature and disposed in unit doses upon patient request, which is defined as one tablet or capsule that is individually packed. In this way, quality of oral anticancer drugs can be guaranteed and any unused single medication units can be returned to the pharmacy, to redispense them to another patient.[32]

Since the Meds Safe is a new invention, more information about the feasibility and cost-benefits of the device must be obtained, prior to decide whether it is suitable for usage in the pharmacy. Patients and pharmacy employees, who will mainly be involved in the use of the medicine locker, have to be contented with the usability and applicability of the device. In addition, logistic costs for implementing the medicine locker, like initial investments related to the device as well as labour time of the pharmacy personnel, must outweigh the costs spared by redispensing unused oral anticancer drugs. Therefore, the aim of the study was to evaluate the feasibility of the Meds Safe and to make an assessment of the operational costs, so that eligible oral anticancer drugs for cost-beneficial redispensing could be identified.

Methods

Study design and setting

The evaluation of the feasibility of the Meds Safe and identification of eligible oral anticancer drugs for redispensing were executed via questionnaires and a micro-costing study in two Dutch outpatient pharmacies, between February and June 2022. The two hospitals included: Radboud university medical center, an academic hospital located in Nijmegen, and Elisabeth Tweesteden Hospital (ETH), an educational hospital located in Tilburg.

Feasibility

Study population

The feasibility of the Meds Safe has been evaluated with patients, treated with oral anticancer drugs, and pharmacy personnel, employed at the outpatient pharmacies of the two Dutch hospitals.

Patients, taking tamoxifen 20mg or lenalidomide (Revlimid®) 10mg, who had at least two prescriptions and regularly picked up their medication at the outpatient pharmacy of the ETH, were asked to participate in the research by phone by the research team. Tamoxifen was used to conduct the technical pilot, since it is a low-priced drug, and Revlimid® was chosen because it is expensive and the treatment only involves 21 tablets. During the phone call, patients received information about the aim of the research, prior to give their oral consent to the study. Patients had time to consider participation, hence, if required, a second phone call was planned. Patients taking tamoxifen 20mg were additionally asked to agree with switching their tamoxifen brand name to Sandoz, if another brand was currently in use. Reasons for not participating in the study were noted, but not mandatory to share. In addition, two pharmacy

employees per participating hospital were asked to participate in the research.

Data collection

Patients – Usability, applicability and experience at home

To examine the feasibility of the Meds Safe, a number of patients who gave their consent to the study, received their anticancer treatment via the Meds Safe for once, after which their opinion about the medicine locker was evaluated through questionnaires.

Patients received instructions about the usage of the Meds Safe at the outpatient pharmacy of the ETH, after which they received one month of their oral anticancer treatment (30 tablets tamoxifen 20mg Sandoz or 21 capsules Revlimid® 10mg) via supply by the Meds Safe. Subsequently, all patients were requested to complete two printed surveys: the first after receiving the Meds Safe (pre) and the second after returning the device to the outpatient pharmacy (post). The pre-questionnaire was completed after the patients got instructions about the Meds Safe and had used the medicine locker for a few days at home. The post-questionnaire was completed after the patients had used the Meds Safe for thirty days, or shorter if the anticancer therapy was discontinued earlier, and had returned the device to the outpatient pharmacy of the ETH. Both questionnaires could be filled in at home and handed in by mail or at the outpatient pharmacy after completing.

Questions, related to the usability and applicability of the Meds Safe, were answered on a 6-point scale with answers ranging from 'strongly disagree' (0) to 'strongly agree' (5). In addition, two questions about the experience of transportation and the location of the Meds Safe at home were answered by multiple choice. The questionnaires were developed using an iterative process. A pilot with the first patients was used to improve the questions regarding the received instructions, usability and contribution to the right use of medicines.

Pharmacy employees – Usability and acceptability

In addition to the patient evaluation, two pharmacy employees per hospital were asked to answer ten statements of the System Usability Scale (SUS), prior to having an oral questionnaire based on the acceptability of the Meds Safe. Both the questionnaire and the interview were completed in separate rooms in the outpatient pharmacies.

The SUS was used to determine the usability of the Meds Safe, as it was previously proven to be reliable for testing usability with a small number of participants.[33-35] Therefore, statements of the SUS-template were used[34], containing five answer options, varying from 'strongly disagree' to 'strongly agree' (supplementary table 1). Subsequently, structured interviews were conducted, based on the seven domains of the Theoretical Framework of Acceptability (TFA).[36] A combination of open- and closed-ended questions was used to obtain insight in the acceptability of the Meds Safe (supplementary table 2). Each interview was recorded and transcribed afterwards, and key points were categorized per answer and corresponding question. Besides, the frequency to which answers were given to closed-ended questions was determined.

Assessment of operational costs

A micro-costing study was performed to get an overview of the operational costs for redispensing oral anticancer drugs. All process steps and recourses required for dispensing and returning the Meds Safe in the pharmacy were identified in detail, followed by an identification of oral anticancer drugs that are eligible for redispensing with the medicine locker.

In collaboration with the manufacturer and a pharmacist employed at ETH, the research team has composed a list of proceedings required for dispensing and returning the Meds Safe in the pharmacy, which will be defined as the dispensing cycle. Only actions that differed from the regular process were noted. A simulation of all proceedings required for the dispensing cycle of the medicine locker was then carried out by the participating pharmacy employees in triplicate. The time of each simulation was measured and eventually plotted in a learning curve, after which the last measurement per pharmacy staff member was considered the most accurate to use in the analysis.[37]

Secondly, costs for all steps required for dispensing and returning the Meds Safe were determined and calculated, including labour, material and overhead costs. Prior to the calculation of the total costs, a list of additional resources needed for the dispensing cycle of the medicine locker in the pharmacy was created, including pharmacy personnel and necessary materials. Subsequently, labour costs were calculated by multiplying the average duration of the simulation with the salaries of the participating pharmacy employees, based on median annual salary.[38-40] Salary scales, of a 36-hour working week and based on 1558 working hours per year, were converted to a per minute rate and increased by 39% for social security contributions.[41] In addition, material costs were based on purchase prices. Since the Meds Safe is still in development, the purchase prices of the device depend on the costs incurred by the manufacturer. Therefore, three scenarios for the costs of the Meds Safe were used in the analysis: €135, €100 and €75, which are the highest, middle and lowest purchase costs for the medicine locker, respectively. Furthermore, power consumption of the device was based on the current electricity prices in The Netherlands (June 2022)[42] and overhead costs were assessed 44% of the direct costs, which consisted of the sum of the labour and material costs, excluding costs for the Meds Safe.[43]

Lastly, the price of an oral anticancer drug unit, at which redispensing with aid of the Meds Safe becomes cost-beneficial, was determined. Several scenarios were taken into account during the calculation, namely: variation in the number of patients who discontinued and had wastage (10-25%)[8, 44-46], variation in the amount of unused drug units (35-65%)[8] and the different scenarios of the Meds Safe. The price level was then calculated by dividing the costs for the dispensing cycle of the Meds Safe with the proportion of unused drug units, which was multiplied by the number of drug units that fit in the Meds Safe. The proportion of unused drug units was determined by multiplying the percentage of patients that discontinued therapy and had wastage with the percentage of unused drug units. When using the mentioned percentages above, the proportion of unused drugs vary between 4% and 16%.

$$Price\ level = \frac{Costs\ for\ one\ dispensing\ cycle\ of\ the\ Meds\ Safe}{Proportion\ of\ unused\ drug\ units * \#drug\ units\ in\ Meds\ Safe}$$

$$Proportion\ of\ unused\ drug\ units = \%patients\ who\ discontinued\ and\ had\ wastage * \%unused\ drug\ units$$

Identification of eligible oral anticancer drugs

For the identification, the research team used practical criteria to determine whether oral anticancer drugs were eligible for redispensing with the Meds Safe. The criteria were established after reaching consensus between a master student, two pharmacists and a researcher. Subsequently, it was examined whether branded oral anticancer drugs, from a list of first filling prescriptions from the outpatient pharmacy of the Radboud university medical center between between 1 December 2020 and 31 May 2021, met the formulated criteria. In addition, the number of drug users in 2021[47] were established to determine which oral anticancer drugs are frequently prescribed and thus more favourable to dispense with the Meds Safe. Furthermore, tablet prices were noted according to current drug prices in the Dutch health care system in euros (June 2022).[48] Tablet prices of oral anticancer drugs, which met all practical criteria, were then compared with the calculated price levels from the different scenarios. Since the Meds Safe is still in development, only drugs that met the calculated price levels of all scenarios were identified as eligible for cost-beneficial redispensing with the Meds Safe.

Data analysis

Data has been analyzed by a micro-costing analysis in Microsoft Office Excel 2016 and a descriptive analysis with aid of SPSS Statistics 25. Outcomes were presented as medians with interquartile range (IQR), means with standard deviations (±SD) or minimum and maximum values. Percentages were used to present proportions.

The employees' SUS scores were calculated by converting the given answers into points,

summing up and multiplying by 2.5. Scores were expressed on a scale from 0-100, at which a higher score corresponds with a higher user-friendliness.[49, 50]

Furthermore, a sensitivity analysis was conducted to determine how the price level was affected by different values of the input variables. Included variables were all labour- and material costs for dispensing and returning the Meds Safe, the number of dispensed medications and the proportion of unused drug units. The price level was determined for a best-, base- and worst-case scenario, at which the costs for the Meds Safe amounted €100. The base case (100%) of the other costs included all values that were defined during the assessment of the operational costs. The number of dispensed drug units was set on thirty, as this is the maximum amount of drug units that fit in the Meds Safe, and the proportion of unused drug units was assessed on 8%, after multiplying the middle percentage of the patients who discontinued and had wastage with the middle percentage of unused drug units. The best- and worst-case of the costs were defined at 125% and 75% of the base case, respectively. For the variables other than costs, the best- and worst-case scenarios were reversed, since a higher amount of dispensed and unused drug units will allow more drug units to be redispensed and therefore positively influence the price level at which redispensing becomes cost-beneficial.

Results

Feasibility

Patients

42 patients who used tamoxifen or lenalidomide were contacted by phone to participate in the research. 11 of the 28 patients who used tamoxifen (39%) and 4 of the 14 patients who used lenalidomide (24%) agreed to participate, so a total of fifteen eligible patients (36%) give their consent to the study (table 1). The main reasons for not participating included having no interest in the study, discontinuing the current therapy and not wanting to switch their tamoxifen brand name to Sandoz. Patients' age ranged from 35 to 84 years and thirteen (87%) participants were female.

Table 1: Patient characteristics of participants from usability questionnaire

Characteristic	Patients (n=15)
Gender n (%)	
Female	13 (87)
Male	2 (13)
Age (in years)	
Minimum	35
Maximum	84
Oral anticancer drug n (%)	
Tamoxifen 20mg	11 (73)
Lenalidomide 10mg	4 (37)

All participating patients completed the pre- and post-questionnaire about the feasibility of the Meds Safe (figure 1). Median scores of three and higher were reported for nearly all statements. Only for the "sound of the device is tolerable" of the post-questionnaire, the median score amounted 0 (IQR 0-3), corresponding to a strongly disagreement with the statement. Moreover, the score of this statement differs from the median score of the pre-questionnaire, which amounted 3 (IQR 2-4). Furthermore, a difference was noted for "shape of the device is good", as the score increased from 3 (IQR 3-5) to 4 (IQR 3-5). In addition, the score of the post-questionnaire of "device provides a safe feeling when taking medication" decreased to 3 (IQR 3-5), whereas the score of "process leads to less environmental pollution" increased to 4 (IQR 1-5), compared to the scores of the pre-questionnaire of 4 (IQR 2-5) and 3 (IQR 0-5), respectively.

Additionally, the multiple-choice questions showed that 33% of the patients experienced the transportation of the device as easy and 40% as no different than usual. Nevertheless, patients who came to the hospital by bicycle or public transport, found the transport uncomfortable (13%) or heavy (13%) (figure 2). Once home, patients placed the Meds Safe at different rooms in the house, with the device most often placed in a guest- or study room (47%) due to the disturbing noise of the device (figure 3).

Figure 1: Feasibility of the Meds Safe. Medians with interquartile range for each statement of the pre- (blue, solid) and post-questionnaire (orange, dashed) are presented on a scale from 0 (strongly disagree) to 5 (strongly agree). Number of participants who completed each statement are reported by 'n'.
*Statements have been converted to positive statements and median scores with interquartile range were reversed.

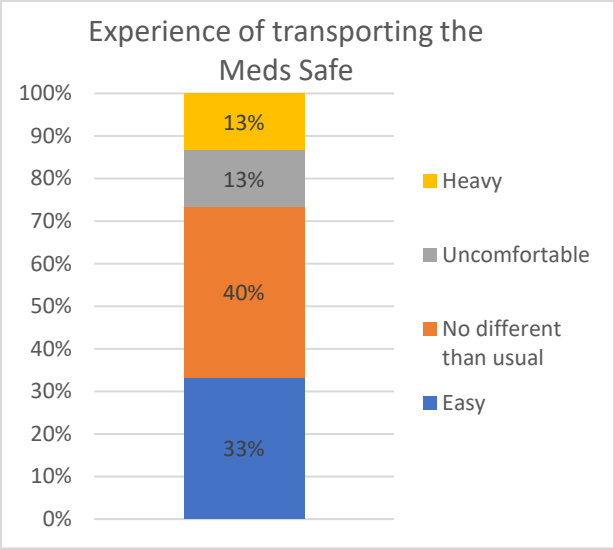

Figure 2: Experience of transporting the Meds Safe

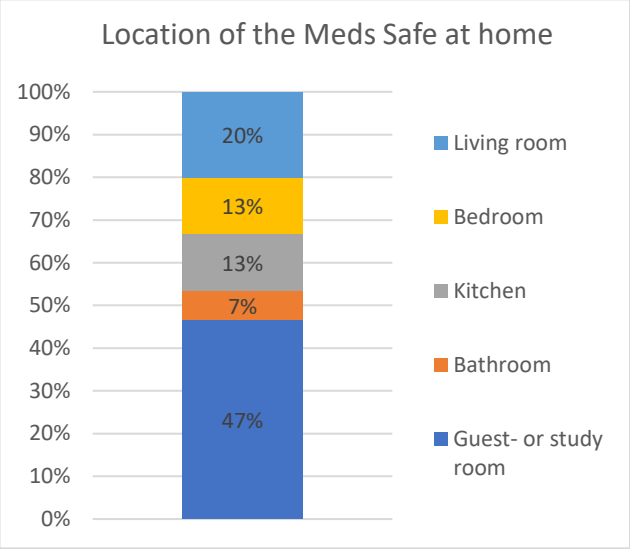

Figure 3: Location of the Meds Safe at home

Pharmacy employees

All participating pharmacy employees completed the SUS and had a median SUS score of 82.5 (IQR 71.3 – 93.1) (supplementary figure 1). Moreover, the SUS scores of the pharmacy employees of the ETH are both higher than the scores of the Radboud university medical center personnel.

Redispensing and the Meds Safe

Additionally, the four employees see redispensing as an important concept, since it can combat drug waste, save costs and prevent environmental pollution. Moreover, they think that the Meds Safe can contribute to counteract drug waste (n=4), especially for expensive drugs that are frequently wasted, as the device can guarantee unused drugs' quality and is easy to use. Nevertheless, disadvantages of the Meds Safe were also mentioned and included: big size, heavy, needed power consumption and limited amount of drug units that fit in the device. Consequently, the medicine locker is not recommended by three employees, as the device firstly has to be more user-friendly. One employee, however, would still recommend the device to combat drug waste.

The dispensing cycle

The dispensing and returning process was experienced as easy and independently executable (n=4), with the checklist as an useful tool to be able to tell all important information about the Meds Safe to the patients (n=2). Although performing the dispensing cycle takes more time than the regular process (n=4), it is not considered to be a significant disadvantage (n=3), as it will saves money and affects the other tasks barely. Conversely, one employee mentioned that the waiting time in the pharmacy could possibly increase.

Assessment of operational costs

Labour costs

After consultation with the manufacturer and the pharmacist of ETH, the research team has composed a list of fifteen additional steps required for dispensing and returning the Meds Safe in the pharmacy, compared to the regular process. Pharmacists, pharmacy technicians and financial assistants were involved in the dispensing cycle, with associated average labour time of 0.4, 7.0 and 11.1 minutes, respectively. The total time it took to perform these extra steps was 18.5 minutes on average (SD ± 3.7), relating to total labour costs of €9.02 based on the costs stated in Table 2. A detailed overview of the measured process steps and corresponding costs is shown in supplementary table 3.

Material costs

Material costs consisted of the purchase price of the Meds Safe, power consumption of the device in the pharmacy and patients' home and the two printed papers needed for dispensing the medicine locker. At a purchase price of €135, the total costs associated with one dispensing cycle were €154, including labour-, material- and overhead costs. If the price of the Meds Safe decreased to €100 and €75, the total costs conducted €119 and €94, respectively.

Table 2: Labour and material costs for one dispensing cycle of the Meds Safe

	Resources	Cost (€)
Labour	**Pharmacist**	0.36
	Pharmacy technician	3.35
	Financial assistant	5.31
Materials	**Meds Safe**	135 - 75
	Power consumption	3.78
	Printed papers	0.05

Sensitivity analysis

The sensitivity analysis showed that the price level is mostly determined by the proportion of unused drug units, the number of dispensed drug units and the purchase price of the Meds Safe. The influence of the labour- and other material costs are comparatively limited (figure 4).

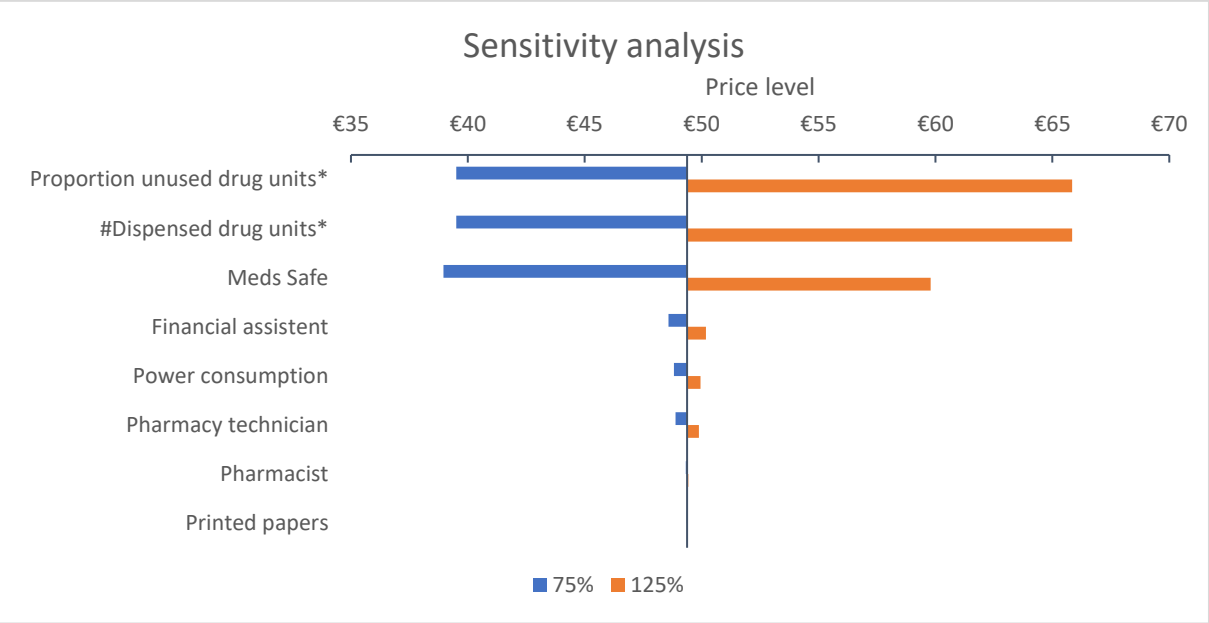

Figure 4: Sensitivity analysis. Influence of the different values of the input variables on the price level is displayed for a best- (75%) and worst-case (125%) scenario. The base case was calculated when the purchase costs of the Meds Safe amounted €100, the proportion of unused drugs was set on 8% and the number dispensed drug units was thirty. Other costs were determined during the assessment of the operational costs. The corresponding price level of the base case is €49.4.
*Best- and worst-case scenario are reversed.

Price level calculation

The price of an oral anticancer drug unit at which redispensing becomes cost-beneficial varied among the different scenarios (figure 5). The price levels were the highest for the scenarios with the highest purchase price of the Meds Safe and decreased when more drug units remain unused. For instance, if the costs of the medicine locker were €135 and 7% of the dispensed drug units would be unused, the price level would be €73.1 and would decrease to €56.4 and €44.5 when the purchase costs of the Meds Safe were reduced to €100 and €75, respectively. Nonetheless, if the price of the Meds Safe remained €135 and the proportion of unused drug units were to rise to 10%, the price level for cost-beneficial redispensing would fall to €51.2.

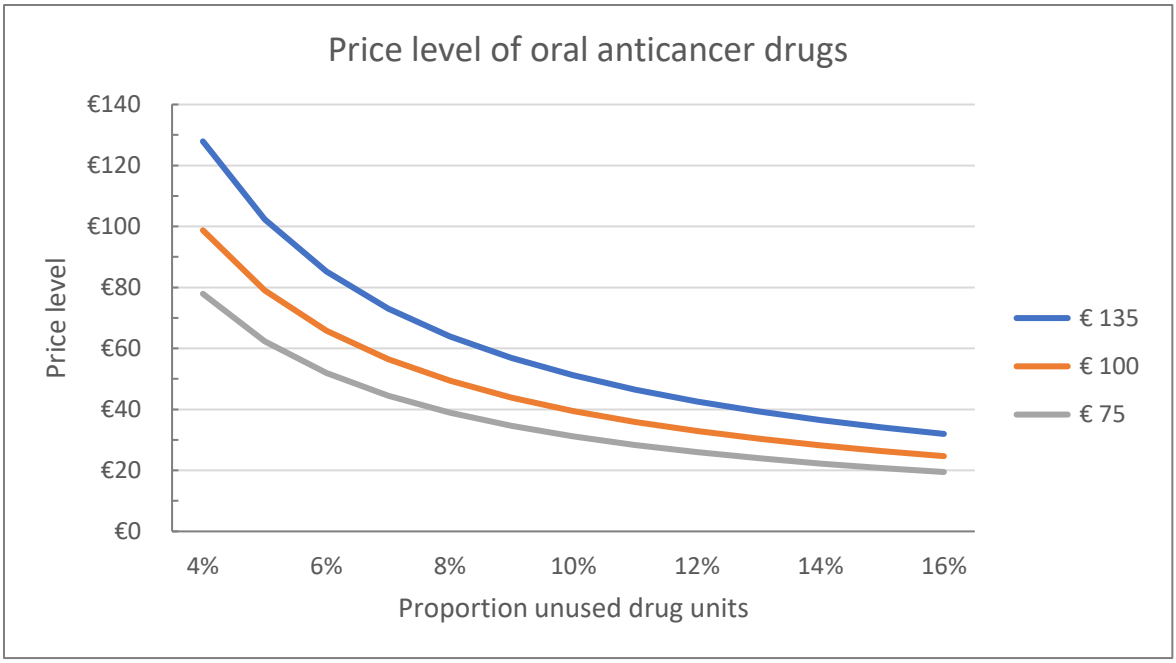

Figure 5: Price level of oral anticancer drugs for cost-beneficial redispensing with aid of the Meds Safe. The price level is plotted against the proportion of unused drug units for different scenarios of the Meds Safe. The proportion of unused drug units was calculated by multiplying the percentage of patients that discontinued and had wastage with the percentage of unused drug units.

Identification of eligible oral anticancer drugs

The following practical criteria were used to identify eligible oral anticancer drugs: 1) packed as a blister package; 2) continuous dosage of one tablet or capsule a day; 3) maximum amount of thirty drug units dispensed at a time and 4) drug patent is valid until at least 01-01-2023.

From the list of first filling prescriptions, six branded oral anticancer drugs meet the practical criteria and have higher tablet prices than the calculated price levels of the different scenarios (supplementary table 4). These drugs are therefore identified as eligible for cost-beneficial redispensing, of which Imbruvica and Tagrisso are most frequently used.

Discussion

In this study, the feasibility of the Meds Safe was evaluated and an assessment of the operational costs was performed to identify eligible oral anticancer drugs for cost-beneficial redispensing. Answers of the pre- and post-questionnaire showed that patients are satisfied with the Meds Safe, except for the disturbing noise of the device. Pharmacy employees also indicated several disadvantages of the device, causing three out of four not recommending the Meds Safe to others. Nevertheless, according to Bangor et al.[51], the Meds Safe can, as a result of the median SUS score, be interpreted as 'acceptable'. Besides, the score corresponds with a 'promoter' classification of the Net Promoter Scores (NPS), which means that the pharmacy employees are likely to recommend the medicine locker to relatives.[52] These differences may be explained in the way questions about the feasibility were asked. The SUS score was determined by answers to written statements, whereas the pharmacy personnel were able to answer open-ended questions during the oral questionnaire and were therefore not limited in giving answers. Moreover, pharmacy employees may interpret the questions of the SUS different than the way they were intended[53] and not all questions may fit well with the Meds Safe, since the questions were initially formulated for different types of systems and devices.[34] Additionally, it is interesting to note that the SUS scores of the ETH employees were higher than the scores of the Radboud personnel. A possible explanation is that the ETH employees were involved in the development of the device, causing higher scores to be given. Furthermore, the results show that patients and pharmacy employees find the Meds Safe suitable to counteract drug waste, as the device is easy to use and drugs can be stored in a controlled environment. This accords with previous studies, which stated that

patients are likely to redispense unused drugs, as long as the quality can be assured.[30, 31]

Furthermore, this study identified six high-priced oral anticancer drugs as eligible for redispensing. This is in line with the results of another micro-costing study[27], which showed that redispensing expensive drugs is efficacious to combat drug waste. The study of Bekker et al., however, calculated the price level for medication packages, whereas this study calculated the price level for oral anticancer drug units. The recommendations are therefore not fully comparable. Moreover, due to the minimum number of identified oral anticancer drugs, the application of the Meds Safe in the pharmacy will be limited. Besides, alterations to the legislation and regulations are necessary, since it is currently not possible to redispense medications.[24] Accomplishing these adjustments is, however, only sensible if the medicine locker can be frequently used. As a result, possibilities to expand the implementation of the Meds Safe should be investigated, such as other medications that are eligible for cost-beneficial redispensing or evaluating adherence, as the device can monitor dispensing moments. Furthermore, other ways to counteract medication waste need to be examined, since redispensing alone will not be enough to combat the consequences caused by unused drugs.[14]

A key strength of this study is the formulation of the detailed overview of the process steps, leading to an accurate calculation of the associated costs. In addition, practical criteria were essential to formulate, since the amount of drug units that fit in the Meds Safe is limited, medicines have to be packed appropriately and price negotiations may change the eligibility of identified oral anticancer drugs. Furthermore, only continuous once-daily dosed oral anticancer drugs were identified as eligible for redispensing. This accords with results of Bekker et al.[54], which showed that long-term used medications are more often eligible for redispensing than acute treated drugs.
Additionally, values of the variables in the micro-costing model can be easily adapted in response to adjustments of the Meds Safe. The model can therefore still be used when the device will be further developed, allowing the identification of eligible oral anticancer drugs to be updated.

This study also has some potential limitations. Firstly, the frequency in which reasons for refusal to participate in the feasibility study were given, has not been determined. This may have led to non-response bias, as patients who did not participate in the study may not encourage medication redispensing.[55] The opinion of these patients may therefore be insufficiently reflected in the presented data, leading to more positive results. Moreover, due to the small heterogeneous patient group, the results are not representative of all patients taking oral anticancer drugs. In addition, only patients treated with tamoxifen and lenalidomide were asked to participate in the study. This may have led to selection bias, since the Meds Safe is also intended for drug users, treated with more expensive and frequently wasted oral anticancer drugs. Besides, not all patients answered the same questions of the pre- and post-questionnaire. The results of the feasibility study therefore need to be interpreted with caution, as the results are not generalizable.
Furthermore, a time simulation has been completed with process steps that have not been implemented yet. The proceedings were therefore performed and measured with an approximation of the real process, causing the measured time to may differ from the real time required for performing the dispensing cycle. This approach, however, will barely influence the eligibility of oral anticancer drugs, as the sensitivity analysis showed that the price level is minimally affected by the labour costs. In addition, this study assumed that all unused drug units will be returned to the pharmacy. This may have led to an underestimation of the price level, as not all patients may return the Meds Safe to the outpatient pharmacy, causing less oral anticancer drugs to be eligible for cost-beneficial redispensing. Additionally, Ruddy et al. reported that the adherence to oral anticancer drugs vary significantly[56], since adherence is affected by multiple factors.[57] Due to variation in discontinuation rates, this study used average percentages of patients who discontinued and had wastage and unused drug units. In practice, however, these percentages will not be the same for every oral anticancer drug and may also differ between pharmacies. The advice given in this study may therefore misrepresent the identified drugs. On the other hand, the eligibility of new authorized oral anticancer

drugs for cost-beneficial redispensing with the Meds Safe can be easily examined, since average proportions are used and only unit prices have to be entered into the presented formula. Medicines that have not been analyzed yet, can therefore still be identified in the future.

In conclusion, patients and pharmacy personnel find the Meds Safe suitable for medication redispensing, but not acceptable to use. Moreover, due to the costs and practical criteria that oral anticancer drugs must meet, only six drugs were identified as eligible for cost-beneficial redispensing. Using the Meds Safe in the pharmacy will therefore still be limited. Consequently, adjustments are needed to make the Meds Safe more user-friendly and applicable. When more drug units will fit in the Meds Safe, the price level will decrease, hence more oral anticancer drugs will be eligible for cost-beneficial redispensing.
In the future, to develop a full picture of the feasibility of the Meds Safe, additional research will be needed in a large group of patients treated with oral anticancer drugs. Moreover, only six drugs are identified as eligible, so research into the eligibility of other medicines is needed to enlarge the possibilities of implementing the Meds Safe in the pharmacy.

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Appendix

Supplementary tables

Supplementary table 1: System Usability Scale. Ten statements of the SUS are presented with answers varying from 'strongly disagree' to 'strongly agree'.

1 – I think that I would like to use this device frequently[1]				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
2 – I found the device unnecessarily complex				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
3 – I found the device easy to use				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
4 –I think that I would need the support of a technical person to be able to use the device				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
5 – I found the various functions in this device were well integrated				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
6 – I thought there was too much inconsistency in the device				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
7 – I would imagine that most patients would learn to use this device very quickly				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
8 – I found the device very cumbersome to use				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
9 – I felt very confident using the device				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
10 – I needed to learn a lot of things before I could get going with this device				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree

[1]Statements are modified by replacing the word 'system' with 'device'

Supplementary table 2: Overview of asked questions during the interview about the acceptability of the Meds Safe. Corresponding domains of the Theoretical Framework of Acceptability are presented for each question.

Part 1: Redispensing and the Meds Safe	**Domain**
1. What do you think about redispensing medicines in general?	Affective attitude Ethicality
2. What do you think of the Meds Safe (incl. appearance, usability and practical considerations)?	Affective attitude
3. Do you think the device can help to prevent drug waste? Why?	Perceived effectiveness Ethicality
4. Which drugs do you think are suitable for the Meds Safe? Why?	Affective attitude
5. Would you recommend the device to family/relatives? Why?	Ethicality
Part 2: The dispensing cycle	
1. What do you think of the process of dispensing and returning the Meds Safe? - Is the process clear enough?	Affective attitude Opportunity costs
2. Do you need extra help by dispensing and returning the Meds Safe? - If so, what do you need and how can this be offered to you?	Intervention coherence Self-efficacy
3. Do you have enough information to inform patients about the Meds Safe and the purpose of redispensing? - If not, what else do you want to know?	Intervention coherence Self-efficacy
4. What do you think about the duration of the process? - Does it affect other tasks and if so, how?	Burden Opportunity costs

Supplementary table 3: Overview of process steps required for one dispensing cycle of the Meds Safe in the pharmacy, which differ from the regular process. Mean time in minutes and corresponding costs are presented for each step. All process steps can be performed by a pharmacy technician, unless stated otherwise.

Process steps	**Mean time (minutes)**	**Cost (€)**
Step 1. Order medicines	1.74	0.83
- Order medicines		
Step 2. Receive filled devices from manufacturer	0.21	0.18
- Review delivery and sign order by pharmacist		
Step 3a. Receive prescription	0.13	0.06
- Recognize prescription drug from list "medicines intended for Meds Safe" and write 'Meds Safe' on recipe		
Step 3b. Prepare medication	1.21	0.58
- Take device with correct medicines from the 'ReMediZ closet' and scan QR code on the device. If an error occurs: select **"**opened packaging**"** - Document "RMZ device dispensed" + unique number of the device in the EHR[1] - Pick information brochure and "checklist dispensing Meds Safe" from stack of printed papers - Take the Meds Safe, information brochure, checklist and prescription and guide the patient from the counter to the consultation room		
Step 3c. Dispensing Meds Safe	2.73	1.31
- Inform the patient about the Meds Safe based on the checklist - Put prescription and signed checklist in the pharmacist's tray		
Step 4a. Receive returned devices	0.64	0.31
- Receive returned device from the patient at the counter - Document "RMZ device returned" + unique number of the device in the EHR - Put device back in the 'ReMediZ retour closet' and connect device to the socket		
Step 4b. Sending devices retour	0.74	0.43
- If "ReMediZ retour closet" gets stocked: call manufacturer to make a pick-up appointment - Sign retour order by pharmacist		
Step 4c. Process logistics	11.08	5.31
- Credit unused medication by financial assistant		
Total	**18.5 (SD ± 3.7)**	**9.02**

[1]Electronic Health Record

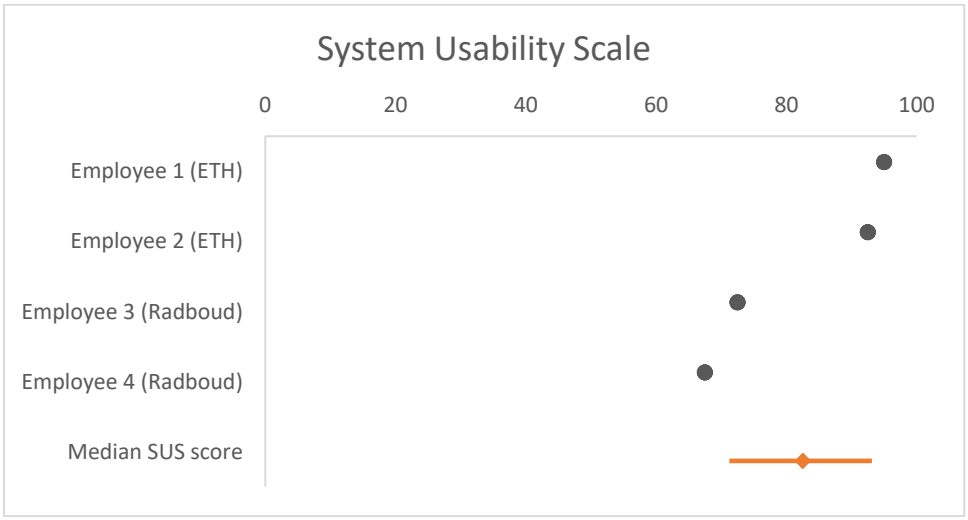
Supplementary table 4: Overview of branded oral anticancer drugs and practical criteria. Active substance, dose, costs for one tablet/capsule and number of users in 2021 is presented for each drug. A 'x' is used to display which oral anticancer drugs met the formulated practical criteria. Oral anticancer drugs that met all practical criteria and the calculated price levels of all scenarios are marked in green.

					Practical criteria			
Name	**Active substance**	**Dose**	**Tablet price**	**Number of drug users in 2021[1]**	**Blister package**	**Continuous once-daily dosed**	**Maximum amount of thirty drug units dispensed**	**Patent is valid till 01-01-2023**
Alecensa	Alectinib	150MG	€ 24,52	214	x			x
Bosulif	Bosutinib	500MG	€ 144,58	117	x	x	x	x
Braftovi	Encorafenib	75MG	€ 37,99	475	x			x
Cabometyx	Cabozantinib	20MG	€ 213,43	267		x	x	x
Cabometyx	Cabozantinib	60MG	€ 213,43	267		x	x	x
Caprelsa	Vandetanib	300MG	€ 187,44	20	x	x	x	x
Endoxan	Cyclophosphamide	50MG	€ 0,67	10,169	x	x	x	x
Erivedge	Vismodegib	150MG	€ 175,35	26			x	x
Glivec	Imatinib	100MG	€ 10,23	1,725	x		x	
Glivec	Imatinib	400MG	€ 47,95	1,725	x	x	x	
Ibrance	Palbociclib	125MG	€ 101,97	2,298	x		x	x
Iclusig	Ponatinib	30MG	€ 196,46	62			x	x
Iclusig	Ponatinib	45MG	€ 196,46	62		x	x	x
Imbruvica	Ibrutinib	140MG	€ 62,43	1,044	x	x		x
Imbruvica	Ibrutinib	280MG	€ 124,86	1,044	x	x		x
Imbruvica	Ibrutinib	420MG	€ 187,30	1,044	x	x	x	x
Imbruvica	Ibrutinib	560MG	€ 249,73	1,044	x	x	x	x
Imnovid	Pomalidomide	2MG	€ 445,88	366	x		x	x
Imnovid	Pomalidomide	4MG	€ 450,10	366	x		x	x
Inlyta	Axitinib	5MG	€ 68,78	50	x		x	x
Jakavi	Ruxolitinib	5MG	€ 31,82	1,389	x		x	x
Jakavi	Ruxolitinib	10MG	€ 63,16	1,389	x		x	x
Jakavi	Ruxolitinib	15MG	€ 63,16	1,389	x		x	x
Jakavi	Ruxolitinib	20MG	€ 63,16	1,389	x		x	x
Lanvis	Tioguanine	40MG	€ 2,57	-[2]				x
Lenvima	Lenvatinib	4MG	€ 64,68	130	x			x
Lenvima	Lenvatinib	10MG	€ 64,68	130	x		x	x
Leukeran	Chlorambucil	2MG	€ 0,48	507			x	x
Lonsurf	Trifluridine/tipiracil	15/6,14MG	€ 30,85	516	x			x
Lonsurf	Trifluridine/tipiracil	20/8,19MG	€ 41,09	516	x			x
Lorviqua	Lorlatinib	100MG	€ 137,74	77	x	x	x	x
Lynparza	Olaparib	100MG	€ 48,37	512	x			x
Lynparza	Olaparib	150MG	€ 48,37	512	x			x
Mekinist	Trametinib	2MG	€ 222,15	620		x	x	x
Mektovi	Binimetinib	15MG	€ 34,18	360	x			x
Natulan	Procarbazine	50MG	€ 6,47	230			x	x
Nexavar	Sorafenib	200MG	€ 33,56	90	x		x	

Purinethol	Mercaptopurine	50mg	€ 0,36	5,677			x	
Revlimid	Lenalidomide	5MG	€ 225,11	3,240	x		x	
Revlimid	Lenalidomide	10MG	€ 233,29	3,240	x		x	
Revlimid	Lenalidomide	15MG	€ 240,70	3,240	x		x	
Revlimid	Lenalidomide	25MG	€ 256,01	3,240	x		x	
Rydapt	Midostaurin	25MG	€ 124,95	49	x		x	x
Sprycel	Dasatinib	70MG	€ 55,59	577		x		
Stivarga	Regorafenib	40MG	€ 40,78	55				x
Sutent	Sunitinib	12,5MG	€ 37,12	409			x	
Tafinlar	Dabrafenib	75MG	€ 52,90	633			x	x
Tagrisso	Osimertinib	80MG	€ 205,01	982	x	x	x	x
Tasigna	Nilotinib	200MG	€ 31,71	377	x			x
Venclyxto	Venetoclax	10MG	€ 5,16	217	x		x	x
Venclyxto	Venetoclax	50MG	€ 25,78	217	x		x	x
Verzenios	Abemaciclib	150MG	€ 46,52	111	x		x	x
Vesanoid	Tretinoin	10MG	€ 4,01	70				x
Votrient	Pazopanib	200MG	€ 25,72	389		x	x	x
Votrient	Pazopanib	400MG	€ 51,00	389		x	x	x
Xalkori	Crizotinib	250MG	€ 85,98	44	x		x	x
Xtandi	Enzalutamide	40MG	€ 28,03	2,819	x			x
Zejula	Niraparib	100MG	€ 96,56	241	x		x	x
Zytiga	Abiraterone	500MG	€ 56,79	2,184	x			

[1]Number of drug users is established per oral anticancer drug. Doses were not taken into account.
[2]Number of drug users is not determined

Supplementary figures



Supplementary Figure 1: System Usability Scale. SUS scores of the participated pharmacy employees of the Elisabeth-Tweesteden Hospital (ETH) and Radboud university medical center are presented on a scale from 0-100. Median SUS Score with interquartile range is displayed in orange.