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Patient-specific blister packaging[1]

Extract

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This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

This investigation on patient-specific blister packaging (PSBP) aims to answer 3 research questions:

- Research question 1: Systemic search and mapping of evidence from prospective studies on PSBP in inpatient and outpatient settings
- Research question 2: Benefit assessment of PSBP in the inpatient (nursing home) setting in comparison with drug dispensing without PSBP, particularly with regard to drug therapy safety and the effects on nurses' professional competence and work-related quality of life
- Research question 3: Comparison of drug dispensing using PSBP in the inpatient (nursing home) setting with drug dispensing without PSBP in terms of the time spent by nursing staff and costs

  To the extent possible, various scenarios and aspects which may influence cost and time spent are considered.

On the basis of the results for research questions 1 to 3, an overall assessment and description of open questions are generated to derive the needs for further research.

Conclusion

PSBP as an option for simplifying drug dispensation to nursing home residents has long been the subject of intensive and controversial discussion. On the one hand, potential advantages of PSBP are cited (e.g. improved drug therapy safety, relief of nursing staff and an associated increase of the individual quality of care, and hence satisfaction of residents with their care). On the other hand, the process is associated with potential problems (e.g. nursing staff losing familiarity with drugs, numerous drugs that cannot be blistered, loss of patient autonomy).

Despite the intensive debate, this Rapid Report found few (7) prospective comparative studies when mapping the evidence on PSBP. Six of these studies were randomized controlled trials (RCTs). All of the studies were conducted in the outpatient setting, and each answered specific research questions (e.g. blister packaging of certain drugs or for patients with specific diseases). None of the studies were conducted in Germany.

No prospective interventional study was found which investigated the research question of interest, the benefit of PSBP in the inpatient (nursing home) setting. Since drug dispensing to patients in these studies differed considerably in the outpatient versus inpatient settings (e.g. regarding medication management and age structure), the results of outpatient studies are not transferable to the inpatient (nursing home) setting. Overall, there is no hint of (greater) benefit or (greater) harm of PSBP in comparison with drug dispensing without PSBP in the inpatient (nursing home) setting.

In addition, insufficient evidence is available on drug dispensation using PSBP in the inpatient (nursing home) setting as regards costs, the time spent by nursing staff, and scenarios (different blistering processes and sites, level of digitization in nursing homes, blister packaging for patients on stable versus unstable regimens, complete or partial blister packaging of the medication with continued need for manual dispensing [certain dosage forms, acute medications] and resources needed when switching medication). The data provided in the literature should be considered highly unreliable. The analysis performed as part of the Rapid Report is based on many assumptions and pragmatic approaches. No sound conclusions can be drawn.

The identified studies described potential cost savings associated with PSBP due to reduced wastage in case of tablet-based (rather than pack-based) billing as well as time savings for nursing staff. Additional expenditures are incurred to the statutory health insurance (SHI) when blister packaging is remunerated. Currently, the billing of blister-packed drugs is not uniformly regulated by law. On the basis of the currently available data, it is difficult to prepare a comprehensive assessment.

Overall, due to a lack of valid data, the cost-effectiveness of drug dispensation using PSBP in the inpatient setting cannot be conclusively assessed. The considerations presented in this report provide examples of the interactions between the remuneration of blistering services and savings due to reduced wastage. Beyond the lack of reliable data, it should be mentioned that it was not possible to consider other care-related expenditures, for example costs incurred to the SHI for outpatient physician contacts or hospitalizations, which may be affected by blister packaging. Further, exclusively the costs of the blistered drugs were considered.

In summary, further research is clearly needed to answer questions about the patient-relevant benefit of PSBP, its effects on nurses' professional competence and work-related quality of life, indicators of drug therapy safety, and economic aspects of blister packaging. Reliable studies must be designed and carried out to determine whether and how the care of patients in nursing homes would be affected by the use of PSBP. To answer the research question of the benefit assessment, an RCT would be preferable. In addition to investigating the benefit and harm of PSBP, such a study could simultaneously determine the costs of care and nurses' time spent. This report includes a suggested study design for such a trial.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AMG	Arzneimittelgesetz (Medicinal Products Act)
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
CI	Confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PSBP	Patient-specific blister packaging
RCT	Randomized controlled trial
SAE	Serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SHI	Statutory health insurance

1 Background

Patient-specific blister packaging (PSBP) refers to the manual or automated repackaging of finished medicinal products upon individual request at pharmacy level in a non-reusable container individualized for patients and their specific dosing times [1]. Pharmacies wishing to offer the service of patient-specific blister packaging have 2 options: They can either perform the blister packaging themselves at the pharmacy or commission a contract manufacturer (known as blister centre) to do so [2,3]. Solid oral dosage forms such as tablets or capsules are generally suitable for blister packaging [4]. The blister packaging of these drugs is performed manually or automatically, usually using a computerized process. Blister packaging is suitable for outpatient and inpatient care and being used internationally [5].

Patient-specific blister packaging has been investigated in several prospective studies [6-8]. However, the value of blister packaging derived from them has been viewed controversially [9,10]. On the one hand, benefits of patient-specific blister packaging are cited (e.g. greater drug therapy safety, relief of nursing staff), but on the other hand, the process is potentially associated with problems (e.g. nurses' loss of competence regarding drugs, numerous drugs not being "blisterable", loss of patient autonomy). No current, independent expert reports are available on this topic. Against this backdrop, the benefit and cost-effectiveness of patient-specific blister packaging in the inpatient (nursing home) setting are assessed in a Rapid Report.

The details of this Rapid Report describe the background in more detail, broken down as follows:

- Introduction to patient-specific blister packaging
- Multidisciplinary drug dispensing process in nursing homes
- Objectives and potential effects of patient-specific blister packaging on drug dispensing (with focus on nursing homes)
- Remuneration for the blistering service

2 Research question

This investigation on patient-specific blister packaging aims to answer 3 research questions:

- Research question 1: Systemic search and mapping of evidence from prospective studies on patient-specific blister packaging in inpatient and outpatient settings
- Research question 2: Benefit assessment of patient-specific blister packaging in the inpatient (nursing home) setting in comparison with drug dispensing without patient-specific blister packaging, particularly with regard to drug therapy safety and the effects on nurses' professional competence and work-related quality of life
- Research question 3: Comparison of drug dispensing using patient-specific blister packaging in the inpatient (nursing home) setting with drug dispensing without patient-specific blister packaging in terms of the time spent by nursing staff and costs

  To the extent possible, various scenarios and aspects which may influence cost and time spent are considered.

On the basis of the results for research questions 1 to 3, an overall assessment and description of open questions are generated to derive the needs for further research.

3 Methods

3.1 Evidence mapping and benefit assessment of PSBP in the inpatient setting (research questions 1 and 2)

Evidence mapping (research question 1)

The evidence mapping included studies with patients in outpatient and inpatient settings, irrespective of illness. The experimental intervention was drug dispensing using patient-specific blister packaging (PSBP). The comparator intervention was drug dispensing without the use of PSBP. Included in the benefit assessment were randomized controlled trials (RCTs) as well as prospective, non-randomized comparative intervention studies with active allocation to groups based on a predefined rule and synchronous control group, and a minimum number of 50 patients in total. Studies with a minimum study duration of 4 weeks were relevant. The included studies were published in the year 2000 or later.

For the evidence mapping, a systematic search for primary literature was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database. The following sources of information and search techniques were also considered: Trial registries and a selection of the bibliographies from identified systematic reviews.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them.

All information necessary for evidence mapping was extracted from the documents on the included studies, entered into standardized tables, and then summarized. For evidence mapping, the included studies were not assessed with regard to certainty of either results or conclusions.

Benefit assessment (research question 2)

On the basis of the studies identified from evidence mapping, the benefit of PSBP in the inpatient (nursing home) setting was to be assessed. The target population of the benefit assessment was restricted to patients in the inpatient setting. The study arms (drug dispensing with or without PSBP) were to differ only in the use of PSBP. Studies of a minimum duration of 6 months were relevant. Non-randomized, comparative intervention studies with synchronous control group and active allocation to groups based on a predefined rule were included only if these studies had been adequately controlled for potentially relevant confounders.

The benefit assessment was to consider the following patient-relevant outcomes:

- Mortality
- Morbidity, particularly
  - Indication-specific outcomes (e.g. symptoms)

  - Non-indication-specific outcomes (e.g. health status, activities of daily living)
- Health-related quality of life
- Side effects
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
  - Severe AEs
  - Discontinuation due to AEs
  - AEs following medication errors
  - Other specific AEs (e.g. falls) if applicable

As commissioned, further outcomes were to be considered as well:

- Indicators of drug therapy safety (e.g. use of the wrong drugs or drugs potentially inappropriate for older adults, medication errors [e.g. underdose, overdose, wrong dosing time])
- Nurses' professional competence and work-related quality of life

Since the outcome of treatment adherence is of great importance in investigations on PSBP, adherence results were to be presented as supplementary information in the report and used, if appropriate, in the interpretation of effects on patient-relevant outcomes. However, deriving a benefit on the basis of this outcome alone was not permissible.

The studies identified for evidence mapping were assessed with regard to their relevance for the benefit assessment based on the inclusion criteria listed above. The assessment was performed by 2 persons independently from each other. Any discrepancies were resolved by discussion between them.

All information needed for the benefit assessment was to be extracted from the documents on the included studies and put into standardized tables. The results on the (patient-relevant) outcomes reported in the studies were to be comparatively described in the report.

For each outcome, a conclusion was to be drawn on the evidence for (greater) benefit and (greater) harm. Four categories were available regarding the certainty of conclusions: Proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the 3 scenarios. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

3.2 Assessment of cost-effectiveness (research question 3)

Drug dispensing using PSBP in the inpatient (nursing home) setting was compared to drug dispensing without PSBP in terms of costs and the time spent by nursing staff on the basis of focused information retrieval and an initial search. The target population comprised patients in the inpatient setting, irrespective of illness. The experimental intervention was drug dispensing using PSBP. Both manual and automated blister packaging were included in the consideration. The comparator intervention was drug dispensing without the use of PSBP. Comparative studies or documents containing information on costs or time spent were ideally suited for this purpose. Non-comparative studies or documents containing information on PSBP-related costs and time spent were also taken into consideration. The searches included studies and documents published since the year 2000 without limitation as to healthcare system or country.

Focused information retrieval by studies and relevant systematic reviews was performed in the MEDLINE, Embase, and HTA databases. Authors were queried since information suggesting that a relevant influence on the assessment exists was missing or vague in the available documents. In addition, the documents sent by the BMG were viewed. An initial search was conducted particularly on the scenarios (including epidemiological data). Relevant studies and documents were selected by 1 person. The studies and documents were then reviewed by a 2nd person. Any discrepancies were resolved by discussion between them.

The information necessary for assessing the included studies and documents was extracted into tables. This included study characteristics such as (study) population, (study) setting, data generation, experimental intervention, any comparator intervention, as well as the place and time of the investigation. Tables on costs and the time spent by nurses also included the data sources. Studies were categorized as comparative or non-comparative health economic evaluations and summarized with regard to costs and time spent on the basis of the categories (research question, method, results, classification of results).

The identified cost details and time spent were calculated per unit and included in the considerations regarding cost-effectiveness. In a sensitivity analysis, the relevant parameters were varied. The number of patients eligible for blister packaging in Germany was estimated on the basis of the 2017 Nursing Care Statistics [11], among others. Various scenarios were used to discuss the influence of different parameters of blister packaging on results in terms of costs and possible time savings.

4 Results

4.1 Evidence mapping and benefit assessment of PSBP in the inpatient setting (research questions 1 and 2)

4.1.1 Results of the information retrieval

The systematic search for evidence from prospective studies for evidence mapping of PSBP in outpatient and inpatient settings identified a total of 7 completed studies with 13 associated documents (Bhattacharya 2016 [12], Bosworth 2017 [13], Gutierrez 2017 [14], Lee 2006 [7], Schneider 2008 [6], Simmons 2000 [8], and Valenstein 2011 [15]). No ongoing studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 03/08/2018.

Table 1: Study pool for the evidence mapping – drug dosing using PSBP vs. drug dosing without PSBP, outpatient and inpatient care sectors

Study	**Available documents**	
	Full publication (in professional journals)	**Trial registry entry/results**
Bhattacharya 2016	Yes [12]	No/no
Bosworth 2017	Yes [13,16]	Yes [17]/yes [18]
Gutierrez 2017	Yes [14]	Yes [19]/no
Lee 2006	Yes [7]	Yes [20]/no
Schneider 2008	Yes [6]	No/no
Simmons 2000	Yes [8]	No/no
Valenstein 2011	Yes [15]	Yes [21]/no
PSBP: patient-specific blister packaging; vs.: versus		

4.1.2 Characteristics of the included studies

Studies for evidence mapping

All 7 studies were conducted in the outpatient setting, largely in patients who should be able to self-manage their medications. The studies included adults, typically with specific illnesses (e.g. essential hypertension, hypercholesterolemia, or type 2 diabetes mellitus) in whom PSBP (for 1 or more indicated drugs) was investigated in comparison with conventional drug dosing without PSBP. In some cases, the entire drug regimen was blister-packed (e.g. Lee 2006, Bhattacharya 2016), and in others, only individual drugs were selectively blister-packed (e.g. Scheider 2008, Bosworth 2017). Only Bhattacharya 2016, Lee 2006, and Scheider 2008 included exclusively older patients ($\geq$ 65 years of age). No studies conducted in the inpatient (nursing home) setting were found. None of the 7 studies were conducted in Germany.

Overall, the result of this evidence mapping demonstrates that the effects of PSBP can be and, indeed, have been investigated by means of RCTs, but only in the outpatient setting. Although PSBP is the subject of public debate, particularly for the inpatient (nursing home) setting, no RCTs or randomized comparative intervention studies were found for this setting.

Studies for the benefit assessment

None of the studies identified for the evidence mapping are suitable for assessing the benefit of PSBP in the inpatient (nursing home) setting. This is particularly due to the facts that none of the studies meet the benefit assessment's inclusion criteria and that the results of the identified studies do not answer the benefit assessment's research question. Furthermore, the studies have methodological shortcomings. The reasons for excluding the studies from the benefit assessment are explained below.

Inclusion criteria for the benefit assessment were violated in all studies of the evidence mapping

Table 2 shows which of the benefit assessment's inclusion criteria were violated in the studies identified as part of the evidence mapping.

Table 2: Studies from evidence mapping – violation of the benefit assessment's inclusion criteria

Study	Inpatient setting (nursing home)	Reported patient-relevant outcomes/supplementary outcomes[a]	Study duration was sufficient	Effect of PSBP can be inferred[b]
Bhattacharya 2016	No	Yes/yes (adherence)	No	Yes
Bosworth 2017	No	Yes/yes (adherence)	Yes	No
Gutierrez 2017	No	Yes/yes (adherence)	Yes	Yes
Lee 2006	No	No/yes (adherence)	Yes	No
Schneider 2008	No	Yes/yes (adherence)	Yes	Yes
Simmons 2000	No	No/no	Yes	Yes
Valenstein 2011	No	Yes/yes (adherence)	Yes	No

a: Supplementary outcomes in accordance with discussion in Section 3.1
b: The intervention arm differs from the comparator arm only in the use of PSBP
PSBP: Patient-specific blister packaging

The identified studies are unsuitable for assessing the benefit of PSBP in the inpatient (nursing home) setting; in most cases, this is due to multiple reasons:

- All 7 identified studies (Bhattacharya 2016, Bosworth 2017, Gutierrez 2017, Lee 2006, Schneider 2008, Simmons 2000, Valenstein 2011) were conducted in the outpatient rather than the inpatient (nursing home) setting and are therefore unsuitable for a benefit assessment in the inpatient setting.

- Not all studies investigated patient-relevant outcomes. The Lee 2006 study reported results only for the supplementary outcome of adherence. It therefore remains unclear whether and to what extent conclusions on effects of patient-relevant outcomes can be drawn from the observed effect on the outcome of adherence. The Simmons 2000 study investigated neither patient-relevant outcomes nor supplementary outcomes to be considered as per the commission, but reported results only on surrogate outcomes (e.g. change in blood pressure, change in HbA1c value). These results do not allow drawing any conclusions regarding changes in patient-relevant outcomes. The results of the Simmons 2000 study would therefore be unusable for this research question, irrespective of the investigated care setting. Directly patient-relevant outcomes were surveyed or planned only in the following studies: Bhattacharya 2016, Bosworth 2017, Gutierrez 2017, Schneider 2008, Valenstein 2011.
- With a study duration of 8 weeks, the Bhattacharya 2016 study did not meet the study duration criterion.
- According to the available descriptions of the Bosworth 2017, Valenstein 2011, and Lee 2006 studies, PSBP was used as part of a complex intervention. In these studies, the intervention and comparator arms differed not only in terms of PSBP; rather, the intervention arm included additional measures to simplify or improve drug dosing (typically, more intensive medication management). Any effects on investigated outcomes can therefore not be (exclusively) attributed to PSBP. While it is arguably pointless to use PSBP without medication management, the latter could easily be implemented without PSBP, and would thus be required in the control group as well.

Lack of transferability of the results of studies identified in evidence mapping to the benefit assessment's research question

The description of the studies found in the evidence mapping already shows that these studies investigated patient cohorts and PSBP under framework conditions which materially differed from those of the present research question (residential nursing care) and the German healthcare setting regarding the following aspects:

- Drug dispensing to patients considerably differs between the outpatient setting and the inpatient (nursing home) setting. In the outpatient setting, it is far less structured than in nursing homes. Specifically, this means that patients or their caregivers have to fill prescriptions in a pharmacy (or several pharmacies), organize the proper storage and correct intake of the drugs (themselves), and obtain the prescription refills on time. In nursing homes, this is done by the nursing staff. Since the use of PSBP additionally requires elaborate prescription and medication management, it represents a much greater intrusion into the process of ensuring drug supply for patients receiving outpatient care. For instance, collecting all necessary drugs is far more difficult for patients receiving outpatient care than for patients in nursing homes, for whom updated patient documentation should be routinely available. Consequently, different or more medication errors, with potentially different effects on patient-relevant outcomes, may conceivably

occur in the outpatient sector. Therefore, results from outpatient studies cannot be assumed to be transferable to the inpatient (nursing home) sector.

- The investigated patient cohorts of the identified studies considerably differ from the German nursing home population (e.g. the Gutierrez 2017 study included adults 18 years of age or older who had depression, post-traumatic stress, schizophrenia, or a combination of these diagnoses and who were on at least 1 medication and able to self-manage their medication intake). The studies also used different general conditions for PSBP than are found in the German healthcare setting (e.g. blister-packaging of individual drugs rather than all solid oral drugs used as long-term medication).

Other study limitations

In addition to the major problems of (1) all studies violating the benefit assessment's inclusion criteria and (2) the results from the evidence mapping not being transferable to the benefit assessment's research question, the studies generally suffer from inadequate reporting and presentation of results from the surveyed outcomes. For instance, from among the (large number of planned) secondary outcomes, the Gutierrez 2017 publication reported results only on symptoms (as measured by a change in OQ-45 [Outcome Questionnaire 45 Item Version]) and at unclear and selectively chosen interim time points, but not at the study end (12 months). Further results, e.g. on health-related quality of life (surveyed using the SF 36 [Short Form 36]), are completely missing from the available documents.

In the Schneider 2008 study, the authors report a statistically significant advantage in the PSBP arm for various operationalizations of the outcome of adherence. However, this result is based on an analysis – possibly performed *post hoc* – of some 75% of patients included in the study and is not robust. Regarding secondary patient-relevant outcomes, the Schneider 2008 study merely reported that there was no statistically significant difference in long-term outcomes (e.g. angina pectoris or hospitalization). The publication does not reveal, however, how this survey was conducted.

Summary

Overall, there is no hint of (greater) benefit or (greater) harm of drug dispensing with the aid of PSBP in comparison with drug dispensing without PSBP for the inpatient (nursing home) setting.

4.2 Assessment of cost-effectiveness (research question 3)

In the information retrieval, 11 studies with 14 documents were identified as relevant for assessing cost-effectiveness. The focused information retrieval found 1 publication from Gerber et al. from the year 2008 [22], which relies on an extensive expert report by Lauterbach et al. from the year 2006 [23]. Altogether, 5 studies and documents contained information on cost and/or the time spent by nursing staff in residential long-term care facilities [9,10,23-25]. These included 4 comparative and 1 non-comparative health economic evaluations. No ongoing studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 31/07/2018.

Table 3: Study pool for the assessment of cost-effectiveness

Study	**Available documents ([reference])**
Deutscher Berufsverband für Pflegeberufe 2011	Yes [26]
INPUT Consulting gGmbH 2017	Yes [27]
Lauterbach et al. 2006	Yes [23], [22]
Leker and Kehrel 2011	Yes [24], [28]
Mannel 2011	Yes [29]
Meyer and Kortekamp 2014	Yes [30]
Neubauer and Wick 2011	Yes [25]
Preißner and Höing 2011	Yes [10]
Steinweg Medical GmbH 2011	Yes [31]
Wellenhofer 2012	Yes [32]
Wille and Wolff 2006	Yes [9]

Cost-related data extraction was performed from the perspective of the statutory health insurance (SHI). Costs of €1.60 [9] to €3.00 [23,25] per weekly blister were identified for production of the blister packaging and €1.50 [9] to €3.10 [25] per weekly blister for the pharmacy's blistering service. Savings resulting from reduced wastage due to individual tablet-based (rather than pack-based) billing, which blister packaging makes possible, were reported as 4.1% [23] and 10.6% [24], but using different calculation bases.

Data extraction for the time spent by nurses for drug dispensing in the nursing home was done from the nursing home's perspective. The studies showed time savings related to PSBP. In terms of collecting and counting out the drugs, the median calculated time savings were 165 minutes per ward and week [25]. For coordination, median time savings of 35 minutes and 58 minutes per ward and week were reported [25]. No time savings were found for drug dispensing using PSBP [25]. For all process steps, Preißner and Höing 2011 [10] reported that with PSBP, total median time savings of approximately 15 minutes per week and resident were achieved. These calculations included only the time needed for dispensing solid oral drugs used as long-term medication, which are typically suitable for blister packaging.

On the basis of the information synthesis as well as various limitations due to the lack of data, the considerations regarding cost-effectiveness from the SHI's perspective required multiple assumptions. Assuming a cost of €3.00 per weekly blister and 4.1% savings to the SHI from blistered medications, blister packaging would be cost-neutral starting at a per-resident cost for blistered drugs of €73.17 per week or €3804.88 per year. No further costs to the SHI were considered.

A sensitivity analysis was run with the variables remuneration per weekly blister and savings due to reduced wastage. The results showed that if the remuneration for the blistering service was in the lower range, at €1.50 per week, drug costs in the range of €14.15 to €46.88 per weekly blister would be cost-neutral. Using the same assumptions regarding wastage and a remuneration for the blistering service at the higher end, at €4.50, drug costs per weekly blister would have to be in the range of €42.45 to €140.63 for the blistering service to be cost-effective under the given assumptions.

Further, an extrapolation was carried out to quantify nurses' (non-monetary) time savings per nursing home resident when PSBP was used in drug dispensing. The considerations regarding cost-effectiveness assumed time savings of 10.00 to 15.84 minutes per week and per nursing home resident receiving blister packs. It was assumed that approximately 409 000 to 614 000 of all 818 000 patients under full-time residential nursing care are receiving blistered drugs. Given further assumptions, nurses' time savings due to PSBP were quantified as 21.67 to 51.48 minutes per month and per nursing home resident. No sensitivity analysis was run.

5 Conclusion

PSBP as an option for simplifying drug dispensation to nursing home residents has long been the subject of intensive and controversial discussion. On the one hand, potential advantages of PSBP are cited (e.g. improved drug therapy safety, relief of nursing staff and an associated increase of the individual quality of care, and hence satisfaction of residents with their care). On the other hand, the process is associated with potential problems (e.g. nursing staff losing familiarity with drugs, numerous drugs that cannot be blistered, loss of patient autonomy).

Despite the intensive debate, this Rapid Report found few (7) prospective comparative studies when mapping the evidence on PSBP. Six of these studies were RCTs. All of the studies were conducted in the outpatient setting, and each answered specific research questions (e.g. blister packaging of certain drugs or for patients with specific diseases). None of the studies were conducted in Germany.

No prospective interventional study was found which investigated the research question of interest, the benefit of PSBP in the inpatient (nursing home) setting. Since drug dispensing to patients in these studies differed considerably in the outpatient versus inpatient settings (e.g. regarding medication management and age structure), the results of outpatient studies are not transferable to the inpatient (nursing home) setting. Overall, there is no hint of (greater) benefit or (greater) harm of PSBP in comparison with drug dispensing without PSBP in the inpatient (nursing home) setting.

In addition, insufficient evidence is available on drug dispensation using PSBP in the inpatient (nursing home) setting as regards costs, the time spent by nursing staff, and scenarios (different blistering processes and sites, level of digitization in nursing homes, blister packaging for patients on stable versus unstable regimens, complete or partial blister packaging of the medication with continued need for manual dispensing [certain dosage forms, acute medications] and resources needed when switching medication). The data provided in the literature should be considered highly unreliable. The analysis performed as part of the Rapid Report is based on many assumptions and pragmatic approaches. No sound conclusions can be drawn.

The identified studies described potential cost savings associated with PSBP due to reduced wastage in case of tablet-based (rather than pack-based) billing as well as time savings for nursing staff. Additional expenditures are incurred to the SHI when blister packaging is remunerated. Currently, the billing of blister-packed drugs is not uniformly regulated by law. On the basis of the currently available data, it is difficult to prepare a comprehensive assessment.

Overall, due to a lack of valid data, the cost-effectiveness of drug dispensation using PSBP in the inpatient setting cannot be conclusively assessed. The considerations presented in this report provide examples of the interactions between the remuneration of blistering services and savings due to reduced wastage. Beyond the lack of reliable data, it should be mentioned that it was not possible to consider other care-related expenditures, for example costs incurred to the

SHI for outpatient physician contacts or hospitalizations, which may be affected by blister packaging. Further, exclusively the costs of the blistered drugs were considered.

In summary, further research is clearly needed to answer questions about the patient-relevant benefit of PSBP, its effects on nurses' professional competence and work-related quality of life, indicators of drug therapy safety, and economic aspects of blister packaging. Reliable studies must be designed and carried out to determine whether and how the care of patients in nursing homes would be affected by the use of PSBP. To answer the research question of the benefit assessment, an RCT would be preferable. In addition to investigating the benefit and harm of PSBP, such a study could simultaneously determine the costs of care and nurses' time spent. This report includes a suggested study design for such a trial.

6 References for English extract

Please see full rapid report for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-35-patient-specific-blister-packaging-rapid-report.9561.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

A.1.1 Search strategies for studies on research questions 1 and 2

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to July Week 2 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 24, 2018
- Ovid MEDLINE(R) Daily Update July 24, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 24, 2018

The following filters were adopted:

- Systematic review: Wong [33] – High specificity strategy
- RCT: Lefebvre [34] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	"drug packaging"/
2	"medication systems"/
3	(medication* and (pack*2 or packaging* or container*)).ti,ab.
4	((unit-of-use* or dose* or multidose* or reminder* or blister* or calendar* or tablet*) adj3 (pack*2 or packag* or dispensing*)).ti,ab.
5	(dose* adj1 system?).ti,ab.
6	(medication* adj1 (adherence* or compliance*) adj5 intervention*).ti,ab.
7	((pharmacy-based* or pharmacist*) adj1 intervention*).ti,ab.
8	or/1-7
9	"randomized controlled trial".pt.
10	"controlled clinical trial".pt.
11	(randomized or placebo or randomly or trial or groups).ab.
12	"drug therapy".fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	"cochrane database of systematic reviews".jn.
16	(search or medline or "systematic review").tw.
17	"meta analysis".pt.
18	or/15-17

#	Searches
19	or/14,18
20	and/8,19
21	20 not (comment or editorial).pt.
22	..l/ 21 yr=2000-Current

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search medication*[TIAB] AND (pack[TIAB] OR packs*[TIAB] OR packed*[TIAB] OR packaging*[TIAB] OR container*[TIAB])
#2	Search (unit-of-use*[TIAB] OR dose*[TIAB] OR multidose*[TIAB] OR reminder*[TIAB] OR blister*[TIAB] OR calendar*[TIAB] OR tablet*[TIAB]) AND (pack[TIAB] OR packs*[TIAB] OR packed*[TIAB] OR packag*[TIAB] OR dispensing*[TIAB])
#3	Search "dose system"[TIAB] OR "dose systems"[TIAB]
#4	Search ("medication adherence"[TIAB] OR "medication compliance"[TIAB]) AND intervention*[TIAB]
#5	Search "pharmacy-based intervention"[TIAB] OR "pharmacy-based interventions"[TIAB] OR "pharmacist intervention"[TIAB] OR "pharmacist interventions"[TIAB] OR "pharmacists intervention"[TIAB] OR "pharmacists interventions"[TIAB] OR "pharmacist's intervention"[TIAB] OR "pharmacist's interventions"[TIAB]
#6	Search #1 OR #2 OR #3 OR #4 OR #5
#7	Search clinical trial*[TIAB] OR random*[TIAB] OR placebo[TIAB] OR trial[TI]
#8	Search search[TIAB] OR meta analysis[TIAB] OR MEDLINE[TIAB] OR systematic review[TIAB]
#9	Search #7 OR #8
#10	Search #6 AND #9
#11	Search #10 NOT medline[SB]
#12	Search #11 AND 2000:2018[DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 July 23

The following filters were adopted:

- Systematic review: Wong [33] – High specificity strategy
- RCT: Wong [33] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	"drug packaging"/
2	"blister pack"/
3	(medication* and (pack*2 or packaging* or container*)).ti,ab.
4	((unit-of-use* or dose* or multidose* or reminder* or blister* or calendar* or tablet*) adj3 (pack*2 or packag* or dispensing*)).ti,ab.
5	(dose* adj1 system?).ti,ab.
6	(medication* adj1 (adherence* or compliance*) adj5 intervention*).ti,ab.
7	((pharmacy-based* or pharmacist*) adj1 intervention*).ti,ab.
8	or/1-7
9	(random* or double-blind*).tw.
10	placebo*.mp.
11	or/9-10
12	("meta analysis" or "systematic review" or medline).tw.
13	or/11-12
14	and/8,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not ("conference abstract" or "conference review" or editorial).pt.
18	..l/ 17 yr=2000-Current

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews : Issue 7 of 12, July 2018
- Cochrane Central Register of Controlled Trials : Issue 6 of 12, June 2018

ID	Search
#1	[mh ^"drug packaging"]
#2	[mh ^"medication systems"]
#3	(medication* and (pack or packs* or packed* or packaging* or container*)):ti,ab
#4	((unit-of-use* or dose* or multidose* or reminder* or blister* or calendar* or tablet*) near/3 (pack or packs* or packed* or packag* or dispensing*)):ti,ab
#5	(dose* near/1 (system or systems*)):ti,ab
#6	(medication* near/1 (adherence* or compliance*) near/5 intervention*):ti,ab
#7	((pharmacy-based* or pharmacist*) near/1 intervention*):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	#8 Online Publication Date from Jan 2000 to Jul 2018, in Cochrane Reviews (Reviews and Protocols)
#10	#8 Publication Year from 2000, in Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR drug packaging
2	MeSH DESCRIPTOR medication systems
3	(medication* AND (pack OR packs* OR packed* OR packaging* OR container*))
4	((unit-of-use* OR dose* OR multidose* OR reminder* OR blister* OR calendar* OR tablet*) AND (pack OR packs* OR packed* OR packag* OR dispensing*))
5	(dose* NEAR1 (system OR systems*))
6	(medication* AND (adherence* OR compliance*) AND intervention*)
7	((pharmacy-based* OR pharmacist*) AND intervention*)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) IN HTA FROM 2000 TO 2018

A.1.2Search strategies for studies on research question 3

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to July Week 3 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 30, 2018
- Ovid MEDLINE(R) Daily Update July 30, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 30, 2018

The following filters were adopted:

- Cost-benefit studies: Glanville [35] – Emory University (Grady) filter
- Cost studies: Wilczynski 2004 [36] – Combinations of terms for optimizing sensitivity and specificity: Cost (all articles)

#	**Searches**
1	"drug packaging"/
2	"medication systems"/
3	(medication* and (pack*2 or packaging* or container*)).ti,ab.
4	((unit-of-use* or dose* or multidose* or reminder* or blister* or calendar* or tablet*) adj3 (pack*2 or packag* or dispensing*)).ti,ab.
5	(dose* adj1 system?).ti,ab.
6	(medication* adj1 (adherence* or compliance*) adj5 intervention*).ti,ab.
7	or/1-6
8	(economic* or cost*).ti.
9	"cost benefit analysis"/
10	"treatment outcome"/ and ec.fs.
11	or/8-10
12	11 not ((animals/ not humans/) or letter.pt.)
13	and/7,12
14	exp "costs and cost analysis"/
15	(costs or cost).tw.
16	or/14-15
17	and/7,16
18	or/13,17
19	18 not (comment or editorial).pt.
20	19 and (english or german).lg.
21	..l/ 20 yr=2000-Current

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search medication*[TIAB] AND (pack[TIAB] OR packs*[TIAB] OR packed*[TIAB] OR packaging*[TIAB] OR container*[TIAB])
#2	Search (unit-of-use*[TIAB] OR dose*[TIAB] OR multidose*[TIAB] OR reminder*[TIAB] OR blister*[TIAB] OR calendar*[TIAB] OR tablet*[TIAB]) AND (pack[TIAB] OR packs*[TIAB] OR packed*[TIAB] OR packag*[TIAB] OR dispensing*[TIAB])
#3	Search "dose system"[TIAB] OR "dose systems"[TIAB]
#4	Search ("medication adherence"[TIAB] OR "medication compliance"[TIAB]) AND intervention*[TIAB]
#5	Search #1 OR #2 OR #3 OR #4
#6	Search economic*[TIAB] OR cost*[TIAB]
#7	Search #5 AND #6
#8	Search #7 NOT Medline[SB]
#9	Search #8 AND (english[LA] OR german[LA])
#10	Search #9 AND 2000:2018[DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 July 30

The following filters were adopted:

- Cost and economic studies: McKinlay [37] – Single term with best optimization of sensitivity and specificity: Costs / Economics

#	Searches
1	"drug packaging"/
2	"blister pack"/
3	(medication* and (pack*2 or packaging* or container*)).ti,ab.
4	((unit-of-use* or dose* or multidose* or reminder* or blister* or calendar* or tablet*) adj3 (pack*2 or packag* or dispensing*)).ti,ab.
5	(dose* adj1 system?).ti,ab.
6	(medication* adj1 (adherence* or compliance*) adj5 intervention*).ti,ab.
7	or/1-6
8	cost*.tw.
9	and/7-8
10	9 not medline.cr.
11	10 not (exp animal/ not exp human/)

#	Searches
12	11 not ("conference abstract" or "conference review" or editorial).pt.
13	12 and (english or german).lg.
14	..l/ 13 yr=2000-Current

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR drug packaging
2	MeSH DESCRIPTOR medication systems
3	(medication* AND (pack OR packs* OR packed* OR packaging* OR container*))
4	((unit-of-use* OR dose* OR multidose* OR reminder* OR blister* OR calendar* OR tablet*) AND (pack OR packs* OR packed* OR packag* OR dispensing*))
5	(dose* NEAR1 (system OR systems*))
6	(medication* AND (adherence* OR compliance*) AND intervention*)
7	((pharmacy-based* OR pharmacist*) AND intervention*)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) IN HTA FROM 2000 TO 2018

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategies
blister AND (packaging OR pack OR packs)
(medication packaging OR medication pack OR medication packs OR "medication container" OR dose dispensing OR pharmacist intervention OR pharmacist program OR pharmacy-based intervention OR pharmacy-based program) [TREATMENT]

2. Deutsches Register Klinischer Studien

Provider: Deutsches Institut für Medizinische Dokumentation und Information

- URL: https://www.drks.de/drks_web/navigate.do?navigationId=search
- Type of search: Simple search in “German and English trial attributes”

Search strategies
blister OR blister* OR "medication container" OR "medication adherence" OR "medication compliance" OR pharmacy OR pharmacy* OR pharmacist OR pharmaci*
medication* AND pack*