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BRIEF REPORT

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Proposal for a new study design and endpoint in research on medication history taking

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ABSTRACT

Introduction: Medication history errors at hospital admission are common and effective strategies to improve the quality of medication histories are still being researched. However, studies on new approaches regarding medication history taking are often time-consuming and resource-intensive. The gold standard when evaluating the quality of medication histories is the comparison of a *Best Possible Medication History* to the original. However, this double collection requires significant resources, disrupts clinical procedures, and places an additional burden on patients. Therefore, more efficient study designs need to be explored. We aimed to develop a design for future studies on medication history taking that uses fewer research resources and places less strain on patients and staff.

Discussion: We first identified shortcomings of the established study designs on medication history taking and subsequently defined requirements for a new design. A pragmatic study with an alternative endpoint was identified in a previous literature search. It served as the starting point from which we developed a new study design to assess the quality of approaches to medication history taking. Instead of taking a second medication history, a patient's pre-existing medication document can be used as comparator to determine the quality of the medication history. Furthermore, we defined a new primary endpoint, *i.e.* the *number of updates per patient*. Updates are differences between the newly acquired medication history and the comparator. They include discontinued, initiated, and changed medications. To enhance our proposed design, we recommend a preparatory phase to identify a suitable comparator document, and a baseline phase to assess the current process.

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Conclusion: We propose a more resource-efficient study design with a new endpoint. We plan to test its feasibility and evaluate whether it could enhance the efficacy of research on medication history taking in a pilot project.

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KEYWORDS Medication history taking; study methodology; medication therapy safety; pharmaceutical research; hospital admission

Introduction

The transition from primary to inpatient care is particularly error-prone, mainly due to the limitations regarding cross-sectoral communication and the timely exchange of medication information (Tam et al., 2005). Comprehensive knowledge on a patient's medication is crucial to continue drug therapy and plan future treatments. Additionally, accurate medication histories are needed to identify potential drug-related problems and to interpret a patient's clinical symptoms during diagnosis, since symptoms may be caused, masked or intensified by medications (Fitzgerald, 2009). Therefore, taking a medication history during hospital admission is essential for a safe, uninterrupted drug therapy (Möller et al., 2024). However, in routine care, medication histories are often inaccurate (Caglar et al., 2011; Giannini et al., 2019; Mazer et al., 2011; Sund et al., 2017). It has been shown that medication discrepancies (MD) between the medications taken at home and those prescribed on admission exist in half of all cases (Cornish et al., 2005) and that most of them are caused by medication history errors (Gleason et al., 2010). Between 11% and 59% of these errors are considered clinically relevant and can potentially harm patients (Cornish et al., 2005; Tam et al., 2005). Unfortunately, the current gold-standard research methodology to evaluate new approaches has several disadvantages, such as an additional burden on patients and staff. Alternative study designs that overcome these disadvantages and facilitate research on new ways to take accurate medication histories (Terstegen et al., 2024) are therefore required. In order to promote more resource-efficient research on medication history taking we developed a new study design.

Discussion

Evaluation of the current challenges of study designs

To develop our design, we analysed the challenges in conventional designs: The current methodology for researching medication history taking uses MDs as parameters to determine the quality of medication history (Mueller et al.,

2012; Terstegen et al., 2024). Usually MDs are identified by comparing a medication history with a second medication history taken for the same patient. The gold standard for such comparisons is the 'Best Possible Medication History' (BPMH), which applies a systematic approach and includes at least two sources, one of which must be the patient interview (World Health Organization [WHO], 2014). It is considered the most reliable way to determine an accurate medication history. The high reliability of this approach comes with trade-offs: Firstly, taking several medication histories means additional time for patients due to additional interviews. Also, second interviews have been shown to reveal extra information (Andersen et al., 2003) due to recall bias, as patients might remember all information from the first interview. This can influence study results and lead to misinterpretations. Different professional groups, *e.g.* physicians and pharmacists, have specific perspectives and thus tend to register different medications when taking medication histories (Carow et al., 2012). This variability can be considered a further limitation of the gold standard methodology, as the BPMHs are usually collected by pharmacists.

Also, BPMHs are complex and time-consuming for staff (Meguerditchian et al., 2013), since they require a comprehensive data collection with several sources and a thorough consolidation of the gathered information. To conduct a BPMH, a certain level of training and experience of the research staff is necessary. Therefore, this method requires significant research resources, which are already scarce. Under real-world conditions, second interviews interrupt clinical procedures, thus causing additional workloads for staff or delaying patient treatment. Ideally, investigators should be constantly available to conduct these interviews, which can be even more time-consuming and decreases internal validity through lack of standardised procedures. Conversely, adapting settings for study purposes can lead to artefactual, study-specific results that do not reflect the reality of clinical practice, thus limiting transferability (Ferguson, 2004) (Figure 1).

Evaluation of alternative study designs

In 2019, Kripalani and co-workers proposed an alternative study design (Kripalani et al., 2019) in which the endpoint for measuring the quality of the medication histories was *whether or not changes to the patients' existing pre-visit medication list (PVML) were made*. Hence, the new medication history was compared with an existing document (PVML) instead of a simultaneously acquired BPMH. The PVML should be a document that is generally available for every patient in the hospital information system. A change (update) was considered a correction and, therefore, an improvement of the medication history. It was hypothesised that more changes were made in the intervention group and that medication history taking was more accurate. The difference between

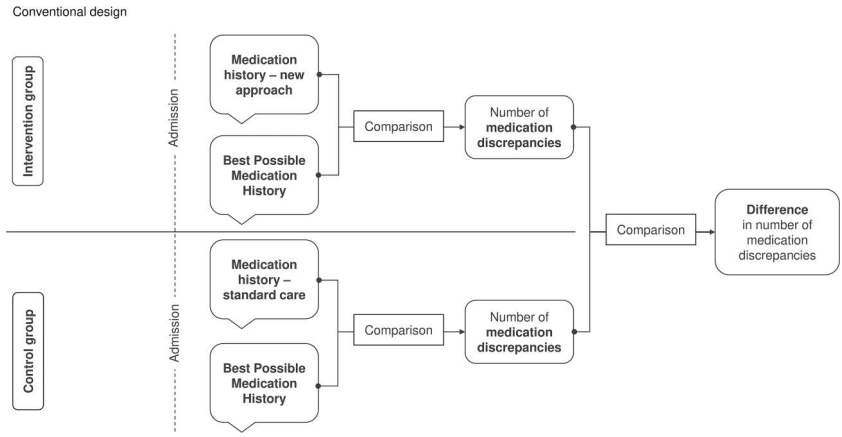

Figure 1. Example of a conventional study design in research on medication history taking. In this design, initial medication histories are taken for patients after hospital admission. Second medication histories (usually BPMHs by an investigator) are taken to serve as the gold standard. The histories for the same patients are compared to generate the number of medication discrepancies for each patient. Intervention group and control group are then compared to calculate the difference in number of medication discrepancies. BPMH: Best Possible Medication History.

the groups in terms of the percentages of patients for whom changes were made to the medication list changed was calculated. Since only one medication history was taken for each patient this approach reduced interruptions, burden on patients, and potential recall bias. Although the approach proved feasible, there are three shortcomings:

To begin with, the study (Kripalani et al., 2019) compared a prospective intervention cohort with a retrospectively matched control cohort (matching criteria: location, intake nurse, Emergency Severity Index). However, a retrospective control group is not always available (*e.g.* due to lack of patient consent) and in a retrospective design relevant factors influencing the results are difficult to determine. Secondly, the endpoint used in the study (Kripalani et al., 2019) is binary and thus does not allow any conclusions about the effect size: A medication history with a single update would be considered equivalent to a medication history with several updates. Lastly, it remains uncertain whether the assumption, that every change to the PVML is a correction of the previous list, is actually true.

Prospective study design

We propose a prospective design with an intervention group and control group (Figure 2). Patients' assignment to a group should be conducted

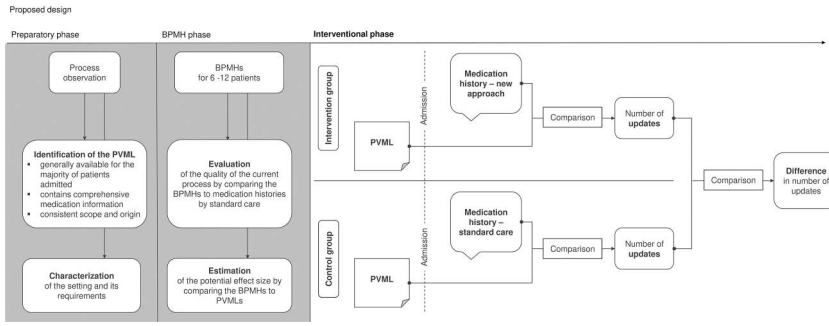

Figure 2. Proposed design. In the proposed design, initial medication histories are taken for patients after hospital admission. A pre-existing document (pre-visit medication list, PVML) will serve as the gold standard for each patient. The initial medication history will be compared to the PVML to determine the number of updates for each patient. Intervention group and control group are then compared to calculate the difference in number of updates. Prior to any intervention, we recommend two additional phases: 1. A preparatory process observation in the target setting to identify and sufficiently define the PVML. It should be a document available for the majority of patients admitted to the study setting that contains comprehensive medication information of consistent scope and origin. This step is crucial, since the type of document is likely to vary between different settings to ensure a standardised outcome measurement. Further, process observations help to characterise the setting and to design an intervention tailored to its requirements. 2. A baseline phase to determine the baseline quality of medication histories and to estimate the potential for improvement in the setting of interest. For this purpose, the current gold standard methodology should be applied: BPMHs are collected for 6–12 patients (usual sample size for preliminary analyses) and compared with the PVML and medication histories recorded in standard care for the same patients.

manually and be stratified according to characteristics that might impact the likelihood of updates. At a minimum, age, sex, the number of PVML-based home medications, and time since the most recent PVML should be considered. The group assignment should be conducted daily to minimise the risk of bias due to different daily schedules. Each patient's medication history should be taken and compared to their respective PVML. To increase internal validity, we recommend two additional phases.

Primary endpoint

The primary endpoint of this study design is the *number of updates per patient*. Updates are differences between the newly recorded medication history and the PVML, a medication document that contains the patients' most recent medication list *before* admission (not the admission medication orders). Such updates could be changes of a patient's drug therapy made in primary care between the current and the previous admission and include discontinued, initiated, and changed medications (including daily dose,

frequency, time of intake, non-interchangeable* dosage form, paused/resumed medication, switch between single-agent products to fixed-dose combination product, and others *e.g.* planned discontinuation). Definitions are provided in Supplement 1, examples in Supplement 2. We further recommend secondary endpoints (Table 1).

Sample size

Since the primary endpoint has not been used in other studies, we conducted a power analysis to investigate the detectable effect with different sample sizes using a non-parametric Mann–Whitney-U test at a two-sided significance level of 5%. Considering an outcome with standard distribution, we suggest a sample size of $n = 75$ per group to be able to detect a standardised effect of $d = 0.5$ with a power of $1\text{-}\beta = 0.826$. The analysis was done using 10,000 simulated data sets in the software PASS v16.0.12.

Statistical analysis

For the intervention phase, comprehensive summary statistics should be provided for baseline characteristics (stratified randomisation characteristics). For the primary and secondary endpoints these should be stratified by group. Two-sided 95%-confidence intervals for differences in means or in rates between groups should be constructed as appropriate. Analyses should include all patients in the group as randomised.

The primary endpoint should be compared between the groups using an analysis of covariance to include relevant confounders in the model that were already accounted for in the stratified randomisation. The significance test based on least-square means with a two-sided significance level of 5%

Table 1. Recommended endpoints.

Primary Endpoint
• Number of updates per patient
Secondary endpoints
• Number of patients with at least one update (yes/no)
• Number of updates in each category
○ Number of updates in discontinued medication
○ Number of updates in initiated medication
○ Number of updates in changed medication
• Number of updates for each subtype in the category 'changed medication'
○ Number of updates daily dose
○ Number of updates frequency
○ Number of updates time of intake
○ Number of updates dosage form
○ Number of updates paused/resumed medication
○ Number of updates single-agent products to fixed-dose combination product (and vice versa)
○ Number of updates other

should be employed. If normal distribution cannot be assumed (visual inspection), a negative binomial model can be considered. Additionally, the primary endpoint should be assessed in different subgroups, which means that an interaction effect of group x subgroup factor is included in the model. The factors considered are sex, age, time since documentation as well as the number of home medications. The binary secondary endpoint 'at least one update' is evaluated by means of a logistic regression model including group as factor and the confounders as specified above. Endpoints for the categories 'medication discontinued' and 'medication changed' can only be analysed in the patient subgroup with at least one medication in the PVML, as otherwise the events (remove, change) cannot occur. All other secondary endpoints should be analysed like the primary endpoint.

Expected strengths of the new study design

The prospective study design should increase the internal validity of future results due to a reduced risk of research biases (selection, observers) and the ability to assess influencing factors (*e.g.* setting-specific conditions). In contrast to conventional study designs in this field, only one medication history is required when using existing documents as comparator. Less staff resources are thus required and the study can be easily integrated in clinical everyday practice without causing interruptions or creating artificial results. Furthermore, the potential recall bias is limited. The suggested additional study phases further increase internal validity: By identifying and sufficiently defining a document to serve as the PVML in a preparatory process observation, a standardised endpoint measurement can be assured. This phase also allows to gather further information on workflows and prerequisites of the given setting, which can be helpful to design a tailored intervention and to identify important factors for its implementation. In addition to the evaluation of the current standard process, results of the BPMH phase can inform sample size calculations and the estimation of effect size.

Expected weaknesses of the new study design

The main weakness of our design remains the interpretation of the primary endpoint as previously mentioned (Kripalani et al., 2019): The assumption that every update is a correction of the previous list holds the risk that mistakes made during medication history taking will be considered corrections as well. Also, the quality of medication histories without updates would always be considered inferior to those with updates. It is therefore crucial to precisely define the scope of medication history taking in order to avoid

artificially inflated differences. We recommend to always include prescription and non-prescription medication. However, it might be necessary to include or exclude supplements or herbal preparations in the analysis, depending on whether they are recorded as per default by standard care in a certain setting. This flaw could be limited further by always applying secondary-source-verification (*e.g.* the PVML itself), which is generally recommended for medication history taking (WHO, 2014).

Since our endpoint relies on the availability of a pre-existing medication documentation, patients without documentation cannot be included in the study. This might limit patient recruitment and skew study results. Conversely, with the PVML as comparator, our design is especially suitable for settings with patients requiring frequent hospitalisations (and, hence, available medication documentation from previous visits) or for settings with EHR data from primary care. With increasing data exchange across different healthcare sectors and defined standards for medication documentation, this requirement is likely to become less limiting in the future.

Conclusion

We propose a new study design and endpoint for research in medication history taking, that provides an efficient alternative to assess the quality of medication history taking. Our approach could help to advance research projects in medication history taking as it allows a quick evaluation with fewer research resources required. This design causes minimal burden on patients and less disruption to workflows and can therefore be easily integrated into everyday clinical practice. Our study design will be applied in a pilot study to determine its feasibility, resource-efficiency and validity against the current gold standard, *i.e.* the BPMH method.

Authors' contributions

Theresa Terstegen: Conceptualisation, methodology, writing – original draft, visualisation; *Marietta Kirchner*: Formal analysis, writing – original draft; *Walter Emil Haefeli*: Supervision; writing – review & editing; *Hanna Seidling*: Conceptualisation, methodology, supervision; writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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