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Impact of a clinical decision support system on paediatric drug dose prescribing: a randomised within-subject simulation trial

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ABSTRACT

Background Drug dosing errors are among the most frequent causes of preventable harm in paediatrics. Due to the complexity of paediatric pharmacotherapy and the working conditions in healthcare, it is not surprising that human factor is a well-described source of error. Thus, a clinical decision support system (CDSS) that supports healthcare professionals (HCP) during the dose prescribing step provides a promising strategy for error prevention.

Methods The aim of the trial was to simulate the dose derivation step during the prescribing process. HCPs were asked to derive dosages for 18 hypothetical patient cases. We compared the CDSS PEDeDose, which provides a built-in dose calculator to the Summary of Product Characteristics (SmPC) used together with a pocket calculator in a randomised within-subject trial. We assessed the number of dose calculation errors and the time needed for calculation. Additionally, the effect of PEDeDose without using the built-in calculator but with a pocket calculator instead was assessed.

Results A total of 52 HCPs participated in the trial. The OR for an erroneous dosage using the CDSS as compared with the SmPC with pocket calculator was 0.08 (95% CI 0.02 to 0.36, p<0.001). Thus, the odds of an error were 12 times higher while using the SmPC. Furthermore, there was a 45% (95% CI 39% to 51%, p<0.001) time reduction when the dosage was derived using the CDSS. The exploratory analysis revealed that using only PEDeDose but without the built-in calculator did not substantially reduce errors.

Conclusion Our results provide robust evidence that the use of the CDSS is safer and more efficient than manual dose derivation in paediatrics. Interestingly, only consulting a dosing database was not sufficient to substantially reduce errors. We are confident the CDSS PEDeDose ensures a higher safety and speeds up the prescribing process in practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Drug dose calculation errors are a well-reported source of preventable harm in paediatrics. Clinical decision support systems (CDSSs) that support prescribers during the dose derivation step seem a promising strategy for error prevention.

WHAT THIS STUDY ADDS

⇒ This simulation study shows that by reducing the human factor during the dose calculation step by using the CDSS PEDeDose, dose calculation errors and dose derivation time can be reduced.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Best practices should include the use of CDSS for dose calculation in children when they have shown to improve the patient's safety. Health authorities and insurances might reward and encourage healthcare providers to use them.

INTRODUCTION

Background and objectives

In paediatric pharmacotherapy, dosing is particularly complex. Historically, clinical trials for regulatory approval were rarely done.[1] Therefore, the available clinical dosing evidence is often limited or of high risk of bias. Thus, most drugs marketed for adults lack approval for paediatric populations and are prescribed off-label.[2 3] Additionally, developmental changes affecting the pharmacokinetics have to be considered when prescribing.[4] As a consequence, paediatric drug dosages are usually calculated individually, mostly based on the child's age, body weight or surface.[5] When considering both, the effort to search for appropriate dosing information and the need to manually calculate individual dosages, it is not surprising that dosing errors are a main cause of preventable harm in paediatric pharmacotherapy.[6–9] Especially in clinical settings, where resources are often limited and timing of a treatment can be critical, the likelihood of human errors is even greater.[10 11] Consequently, there is a need to prevent dosing errors by supporting the physicians that prescribe the dosage as well as the clinical pharmacists that validate the prescriptions. Clinical decision support

systems (CDSS) are thus regarded as a promising strategy to address the unique needs of paediatric pharmacotherapy.[12]

PEDeDose is a CDSS to facilitate drug dosing in paediatrics.[13 14] It provides healthcare professionals (HCPs) with structured dosing information and a built-in dose calculator. The CDSS was developed to prevent dosing errors by either supporting prescribers directly or to validate already prescribed dosages. In accordance with the European Medical Device Regulation, the PEDeus is a certified manufacturer of the class IIa medical device software PEDeDose. A comprehensive description of PEDeDose and its validation has been published previously.[13]

We hypothesised that the use of a CDSS with a built-in dose calculator leads to a reduction of dose calculation errors and makes the dose prescribing step more efficient when compared with manual calculation using a pocket calculator. To assess this, a randomised within-subject simulation trial was conducted, where HCPs were asked to calculate dosages for hypothetical but clinically relevant patient cases.

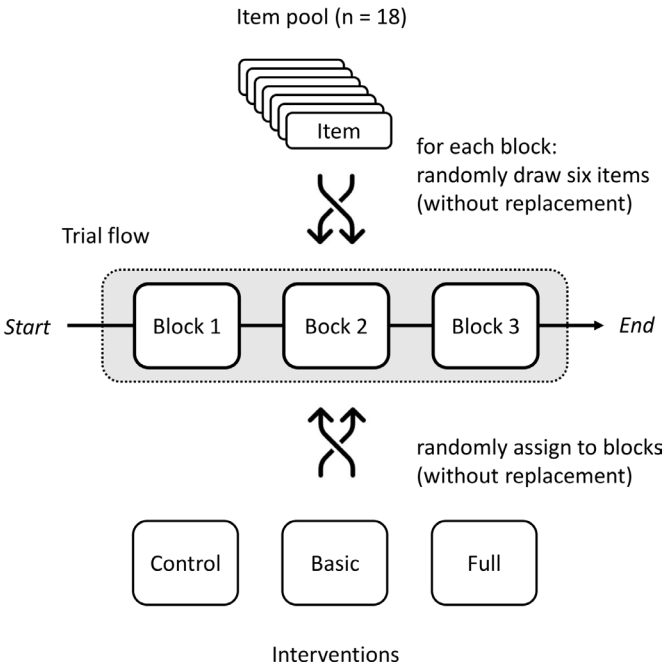

Figure 1 Visualisation of the trial design. The name of the interventions correspond to the CDSS PEDeDose with built-in calculator (full), PEDeDose used together with a pocket calculator (basic), and SmPC used together with a pocket calculator (control). CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

METHODS

Trial design

We conducted a randomised within-subject trial to estimate the impact of the CDSS PEDeDose on the number of dose calculation errors and the time needed for the derivation. As interventions, we defined either the Swiss Summary of Product Characteristics (SmPC)[15] used together with a pocket calculator (control) or the CDSS PEDeDose[14] with its built-in calculator (full). Furthermore, we exploratively assessed the impact of the PEDeDose web application without using the built-in calculator but using a pocket calculator instead (basic). A pool of 18 items, each representing one drug prescription for a hypothetical paediatric patient, was created (online supplemental file 1). The items were developed by the main author (LH) and reviewed by two clinical pharmacists (KK and PV) with extensive experience in the field of paediatrics and neonatology. Only drugs with a paediatric label were selected so that a reference dosage was available in the Swiss SmPC. For each participant the trial consisted of three consecutive blocks. To each block one of the three interventions and six items drawn from the pool were randomly assigned without replacement. The trial design is visualised in figure 1.

We report this study in concordance with the 'Reporting Guidelines for Healthcare Simulation Research: Extensions to the CONSORT and STROBE Statements'.[16 17]

Participants

Our target population consisted of physicians and pharmacists in Switzerland. We focused the recruitment on physicians and pharmacists working in children's hospitals, general hospitals with paediatric clinics and HCPs working in the ambulatory setting that is, public pharmacists and general practitioners. To ensure a high quality of the collected data, the trial was conducted under the supervision of the main author. Participants gave informed consent to the data collection and received a small monetary compensation for their participation.

The participants were mainly recruited via convenience sampling by directly contacting the responsible head of department in Swiss children's hospitals, general hospitals with paediatric clinics or by the company's newsletter. Furthermore, snowball sampling was used as many of the participating HCPs were also helping recruiting their colleagues.

Interventions

The CDSS PEDeDose encompasses a database with general paediatric dosing information and a built-in calculator for individualised dosing. The built-in calculator makes PEDeDose a CDSS. However, the general dosing information can also be consulted without using the built-in calculator. Thus, we defined three interventions: The Swiss SmPC used together with a pocket calculator (control), the CDSS PEDeDose (full) and the PEDeDose dosing information used together with a pocket calculator (basic). The study was powered to compare the CDSS PEDeDose (full) to the SmPC used together with a pocket calculator (control). The SmPC is a full-text electronic resource, while the data of the PEDeDose database is highly structured. Thus, to isolate the effect of structuring drug dosing information, we exploratorily assessed the impact of using PEDeDose

without the built-in calculator. An example of the structured dosing information from PEDeDose is shown in online supplemental file 2.

Simulation setup

The trial was developed using the Gorilla Experiment Builder (www.gorilla.sc), a web-based trial platform.[18] We conducted the trial at the participants workplace. Depending on the availability participants were using their own computers or were provided with a notebook for the trial. The Gorilla website was opened in a browser while the interventions (ie, SmPC or PEDeDose websites) were opened either in a different browser tab or window, depending on the participants preferences. Before the trial started, every participant was briefed about the aim and the design of the trial. Subsequently, the participants were required to solve a dedicated test example with the PEDeDose built-in calculator (full). This ensured that the participants fully understood the capabilities of PEDeDose, such as the possibility to convert the calculated dosage to the correct dosing unit (eg, mg to mL).

Participants were instructed to round the calculated dosage to a maximum of two decimal places. If a dose range was provided by the respective dosing information, participants were asked to submit a range as a result, too.

Outcomes

The primary outcome was the correctness of the derived dosage, a binary variable with 1=error and 0=correct. The secondary outcome was the time needed to solve an item.

Since the dosing information that the participants were required to use was specified in advance and no additional clinical evaluation was required, there was an objectively correct dosage for every item within the corresponding dosing information (SmPC or PEDeDose). Errors were defined as submitted responses that exceeded clinically non-relevant deviations of 5% or 10% for drugs with narrow or wide therapeutic windows, respectively (online supplemental file 1). Even though the participants were required to submit dose ranges as a range, we did not consider it an error if the submitted dosage was a single dosage that was within the correct window. We reviewed all erroneous responses and tried to determine the possible cause of error. For the errors that were found in the full block (ie, PEDeDose with built-in calculator), the logging data of the PEDeDose built-in calculator were additionally analysed. This allowed us to assess whether the participant had specified the calculator inputs incorrectly (ie, drug, indication, route of administration, birthdate, weight, height and gestational age).

The secondary outcome response time was defined as the time difference (in seconds) for each item between the time stamp on the mouse click that initialised item loading and the click that submitted the result. We defined outliers in the time outcome as values greater than three SD for each intervention. We removed outliers and missing values and analysed only complete items.

Covariates

The following categorical participant covariates were assessed prior to the trial start: The type of institution where the participant was working as an unordered factor (children's hospital, general hospital with children's clinic, public pharmacy or doctor's office), their profession (physician, pharmacist), their working experience as an ordered factor (<5 years, 5–10 years, >10 years), and whether they had been already using PEDeDose in their daily work (yes, partly, no).

Sample size

The sample size estimation was done in collaboration with the Clinical Trial Unit of the University of Basel, Switzerland. An a priori error rate of 20% for the control study arm was assumed based on the results of previous research estimating a 26.5% error rate for dose calculation using a pocket calculator.[19] A 50% overall error reduction at a significance level of 5% with >80% power resulted in a total of 600 items that need to be rated. We aimed to test the two arms for the confirmatory analysis with six items per arm, which resulted in an estimated sample size of 50 participants (600 items/12 items per participant=50 participants) (online supplemental file 3). Adding an equal number of items for the exploratory arm, the resulting total number of items that need to be rated was 900, which corresponds to 18 items per participant.

Randomisation

Randomisation was done on the level of the interventions and the items (figure 1). Thus, for each participant the order of the three interventions was randomised, while for each intervention 6 out of the pool of 18 items were randomly drawn without replacement. The Gorilla Experimental Builder enabled to design the randomisation procedure directly into the trial, thus taking care of the participant allocation.[18]

Statistical methods

Statistical analyses were performed in R V.4.1.1.[20] The relevant functions and additional packages used are denoted as function {package}. The only continuous variable was the secondary outcome response time per item, which was transformed using the natural logarithm to achieve normality of the residuals. Orthogonal sum-to-zero contrasts for the unordered factors 'institution' and 'profession' applying contr.sum {stats} were used. The lower-level effects were thus estimated at the level of the grand mean and interpreted accordingly. We applied difference coding for the ordered factors 'experience', 'PEDeDose user' and the exploratory version of the variable 'intervention' using contr.sdif {MASS}.[21] Thus, each level of the ordered factors was compared with their previous level. The contrast coding scheme is provided in online supplemental file 4.

For the primary outcome 'error', we fitted a generalised linear mixed-effects model (GLMM) with a logit-link

function using *glmer* {lme4}.[22] The secondary outcome 'time' was assessed by fitting a linear mixed-effects model (LMM) using *lmer* {lmerTest}.[23] All models were derived by starting with maximal model specification based on the trial design, and then sequentially reducing model complexity until a non-singular fit was achieved.[24] We started by defining by-subject and by-item random intercepts and slopes (ie, crossed-random effects) on each type of intervention. The main variable 'intervention' and the additional covariates were treated as fixed variables.

In exploratory analyses, we assessed the impact of structuring the dosing information by adding the intervention basic (ie, PEDeDose without the built-in calculator). Thus, the binary variable for the intervention became an ordered three-level factor (control, basic, full). As a sensitivity analysis, we created a model that is only adjusted for the order of the interventions.

For all models also an unadjusted model was built, containing only the variable 'intervention' as well as only random intercepts for both subject and item, respectively. We derived Wald confidence intervals. The p values for the linear models were derived via Satterthwaite's df method.[23] The estimated marginal means for the 'intervention' variable for all the models were calculated using *emmeans* {emmeans}.[25] The summary outputs of the models are reported in online supplemental file 2.

RESULTS

Participants

In total, 53 HCPs participated in the study from January to July 2022. One participant was excluded because of non-adherence to the protocol by solving all items using PEDeDose with its built-in calculator. Thus, a final sample of 52 participants was included. The participant flow and randomisation order are visualised in figure 2.

The characteristics of the participants are summarised in table 1.

Missing values and outliers

Of the total 936 items rated, there were 4 responses (0.4%) classified as missing, three in the full intervention, which were accidentally skipped and 1 in the control intervention, where a string was entered instead of a number. For the time outcome, there were in total six samples (0.6%) not analysed, consisting of the four missing responses and two outliers, one in the full intervention and one in the control intervention. The removal of the outliers was justified by the fact that some participants were required to respond to phone calls related to their clinical work.

Numbers analysed

Overall, 932 items were analysed for the primary outcome, which corresponds to 311, 312 and 309 items for the interventions control, basic and full, respectively. For the secondary outcome, 930 items were analysed, which corresponds to 310, 312 and 308 items for the interventions control, basic and full, respectively. The number of errors and median time per intervention are depicted in figure 3 and figure 4, respectively. The total number of errors was 70 (22%), 49 (16%) and 14

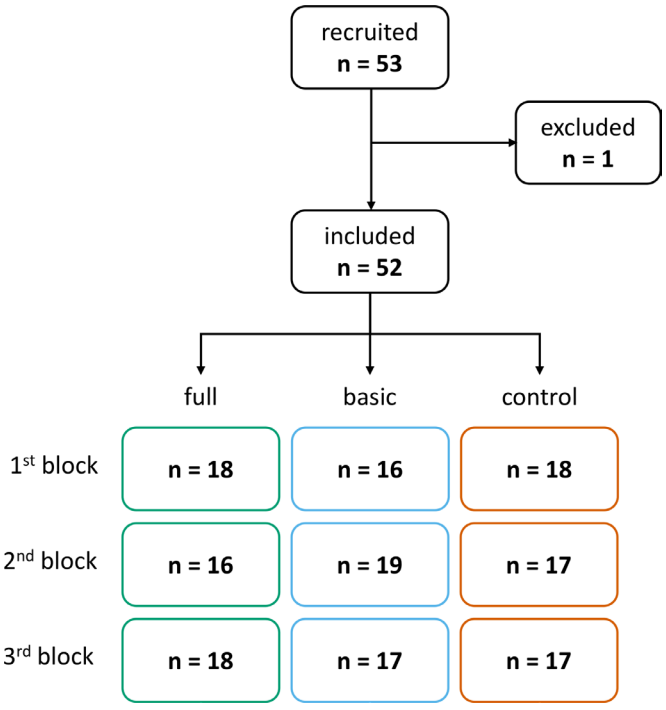

Figure 2 Participant flow chart. The order of the interventions and the corresponding number of participants assigned is shown as well. The name of the interventions correspond to the CDSS PEDeDose with built-in calculator (full), PEDeDose used together with a pocket calculator (basic) and SmPC with pocket calculator (control). CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

Table 1 Participant characteristics

Variable names	No (%)
Participants (total)	52 (100)
Institution	
Children's hospital	21 (40)
General hospital with children's clinic	20 (39)
Public pharmacy/doctor's office	11 (21)
Profession	
Physician	20 (38)
Pharmacist	32 (62)
Experience	
<5 years	20 (39)
5–10 years	20 (39)
>10 years	12 (22)
PEDeDose user	
No	20 (39)
Partly	11 (21)
Yes	21 (40)

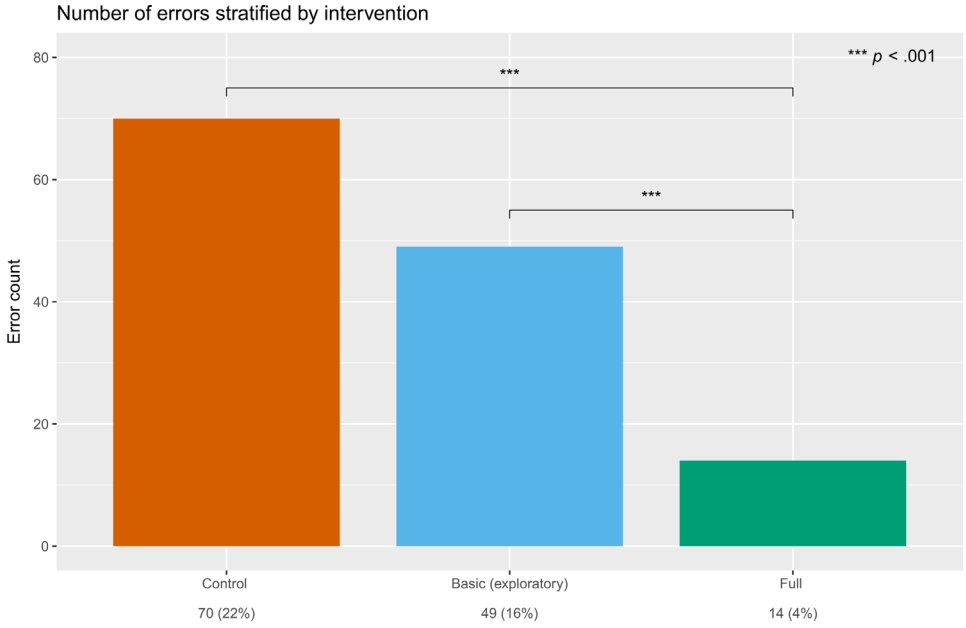

Figure 3 Bar plot depicting the number of errors stratified by the type of intervention. The name of the interventions correspond to the CDSS PEDeDose with built-in calculator (full), PEDeDose used together with a pocket calculator (basic) and SmPC with pocket calculator (control). CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

(5%) errors for the control, basic and full intervention, respectively. The median time (Q_1, Q_3) needed for the dose derivation was 161 s (118, 225), 132 s (96, 173) and 86 s (67, 116) seconds for the control, basic (exploratory) and full intervention, respectively. Figure 5 depicts the number of errors stratified by intervention order and type.

Model estimations

A generalised linear mixed-effects model with a logit-link was defined to estimate the adjusted odds ratio (OR) for dose derivation errors. The regression formula for the generalised linear mixed-effects model is shown below in R notation (I). The model included the covariates

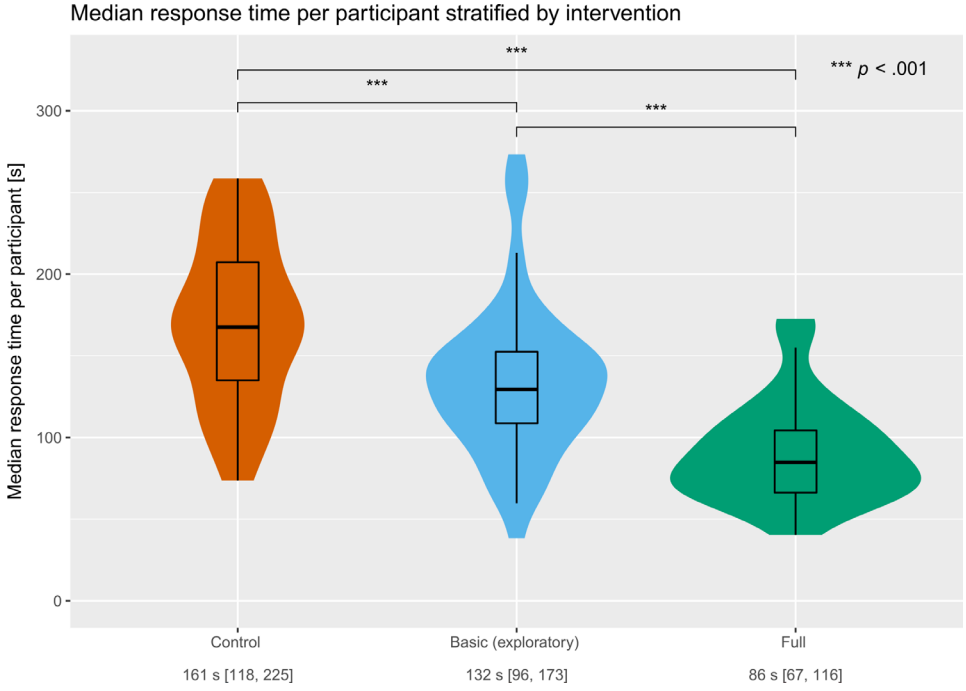

Figure 4 Violin plot depicting the median time per participant stratified by the type of intervention. The violin plot depicts the distribution of the datapoints and is mirrored on the y-axis. Below each plot the overall median (Q1, Q3) of the intervention is shown. The name of the interventions correspond to CDSS PEDeDose with built-in calculator (full), PEDeDose used together with a pocket calculator (basic) and SmPC with pocket calculator (control). CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

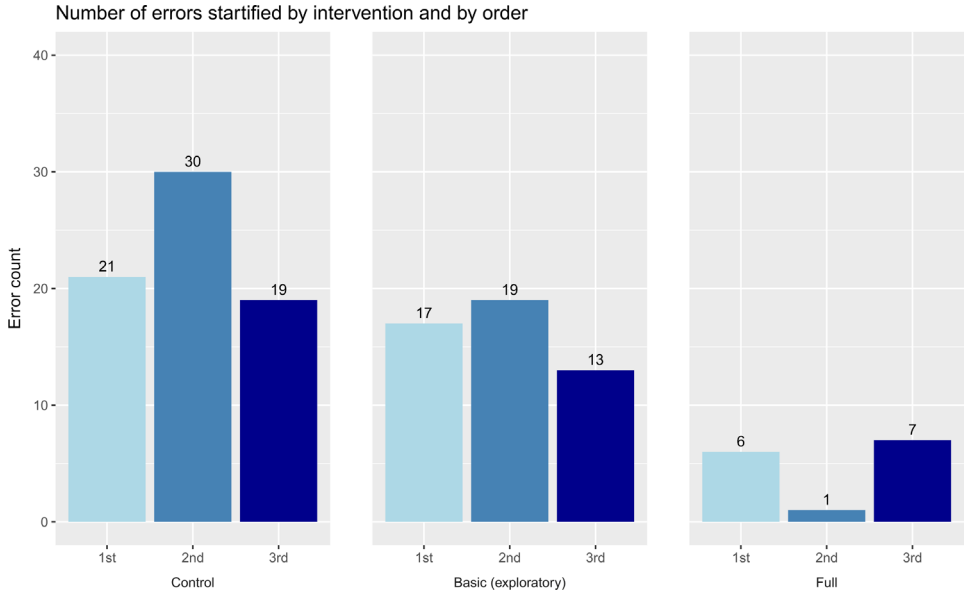

Figure 5 Number of errors stratified by intervention order and type. The name of the interventions correspond to the CDSS PEDeDose with built-in calculator (full), PEDeDose used together with a pocket calculator (basic) and SmPC with pocket calculator (control). CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

for institution and previous PEDeDose user. Experience was not included because of singularity. Profession was not included due to potential multicollinearity with the variable institution as almost all physicians were working in a Children's hospital. No crude difference between the different professions was observed. We used a linear mixed-effects model for the time outcome. The model was built with the same covariates as before but including experience, as there was no issue with singularity (II). The results of the multivariable models are depicted in table 2.

(I) *error~intervention + institution+user (intervention | subject) + (intervention | item)*

(II) *log(time) ~ intervention + institution+experience + user + (intervention | subject) + (intervention | item)*

Additional results of the models are reported in online supplemental file 4.

Ancillary analyses

Exploratory analyses

Additionally, we explored the impact of using structured dosing information while using a pocket calculator. The model formula of the generalised linear mixed-effects model (III) and the linear mixed-effects model (IV) for error and time, respectively, are shown below. Due to singularity, we had to exclude the random slopes for both item and subject. The results of the multivariable models of the exploratory analysis are depicted in table 3. The odds of an error were 4.5 times higher for the basic intervention as compared with of full. Also the odds of an error were 1.4 times higher for the control intervention than for basic. The sensitivity analysis did not indicate that the intervention order influenced the number of errors (online supplemental file 4).

(III) *error~intervention + institution+user + (1 | subject) + (1 | item)*

(IV) *log(time) ~ intervention + institution+experience + user + (intervention | subject) + (intervention | item)*

Additional results of the models are reported in online supplemental file 4.

Analysis of error types

For each error that occurred, we assumed the most plausible error type. The logging data of the PEDeDose built-in calculator was used to improve the determination of the error type in the full intervention. The results of the analysis of error types are provided in table 4.

DISCUSSION

In this simulation trial, we showed that the CDSS PEDeDose (full) significantly reduced the number of dose calculation errors and was more efficient when compared with either the structured PEDeDose dosing information (basic) or the full-text SmPC (control) used together with a pocket calculator.

Strengths and limitations

A general limitation of simulation studies is the lack of control over the participants' mindset. For this study, it means that the participants might not have been as careful while deriving the dosages as they would be while working with real patients. We tried to address this limitation by comparing the interventions within each participant and by conducting the trial at their workplace. Randomisation of the interventions per block as well as on item-level controlled for biases of allocation. Additionally, we see the use of a within-subject design as a major strength of this study as it accounts for subject specific characteristics

Table 2 Effect of the intervention on error and time

Errors			
	OR	**95% CI**	**P value**
Multivariable model			
Intervention full *vs* **control**	0.08	0.02 to 0.36	<0.001
Institution Children's hospital	1.27	0.75 to 2.15	0.382
Institution General hospital	1.12	0.74 to 1.70	0.587
PEDeDose user partly *vs* **no**	0.57	0.27 to 1.29	0.178
PEDeDose user yes *vs* **partly**	0.88	0.37 to 2.11	0.771
Unadjusted model			
Intervention full *vs* **control**	0.15	0.08 to 0.27	<0.001
Time			
	Time change (%)	**95% CI**	**P value**
Multivariable model			
Intervention full *vs* **control**	–45	–51 to –39	<0.001
Institution Children's hospital	–18	–26 to –8	<0.001
Institution General hospital	3	–6 to 12	0.585
Experience 5–10 years *vs* **<5 years**	3	–11 to 18	0.722
Experience >10 years *vs* **5–10 years**	1	–16 to 15	0.862
PEDeDose user partly *vs* **no**	6	–9 to 26	0.472
PEDeDose user yes *vs* **partly**	-8	–22 to 9	0.357
Unadjusted model			
Intervention full *vs* **control**	–45	–48 to –42	<0.001

The table shows the results of the confirmatory analyses comparing the CDSS PEDeDose (full) with the SmPC (control). The multivariable and unadjusted models with only the intervention variable and random intercepts for both subject and item are presented. The reference category for each comparison of the ordered categorical variables is marked in bold.
CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

(eg, being good or bad at calculus) and enhances the study's overall power. Our study evaluated the dosing of a single drug for a single indication. In clinical settings, there are often additional considerations necessary (eg, dose adjustments due to renal insufficiency, comorbidities or drug–drug interactions). However, in this study, the impact of the CDSS PEDeDose was evaluated in isolation, what we see as a strength. Since the SmPC was defined as the reference dosing information, only prescriptions for drugs with a paediatric label could be created. In paediatric practice, however, the majority of drugs are prescribed off-label.[3] Thus, to retrieve off-label dosing information additional sources must be consulted, which might even further increase the time needed to derive the appropriate dosage. Furthermore, we found that it was worthwhile to conduct the study on site as the amount of missing data was very low (<2%) for all interventions. The assumed error types should be interpreted carefully as the true cause of error cannot be determined. The types of errors are strongly depending on the item itself and only limited information can be extracted from the participants' response. For example, not every active ingredient has a loading and a maintenance dose that may be confused.

Table 3 Effect of the interventions on error and time

Errors			
	OR	**95% CI**	**P value**
Multivariable model			
Intervention basic *vs* **control**	0.67	0.44 to 1.03	0.068
Intervention full *vs* **basic**	0.22	0.12 to 0.42	<0.001
Institution Children's hospital	1.37	0.9 to 2.08	0.143
Institution General hospital	0.97	0.68 to 1.38	0.860
Experience 5–10 years *vs* **<5 years**	1.36	0.79 to 2.36	0.273
Experience >10 years *vs* **5–10 years**	1.15	0.64 to 2.05	0.644
PEDeDose user partly *vs* **no**	0.51	0.26 to 1.00	0.050
PEDeDose user yes *vs* **partly**	1.33	0.68 to 2.62	0.402
Unadjusted model			
Intervention basic *vs* **control**	0.67	0.44 to 1.02	0.063
Intervention full *vs* **basic**	0.22	0.12 to 0.41	<0.001
Time			
	Time change (%)	**95% CI**	***p*-value**
Multivariable model			
Intervention basic *vs* **control**	–20	–27 to –12	<0.001
Intervention full *vs* **basic**	–31	–38 to –23	<0.001
Institution Children's hospital	–18	–26 to –10	<0.001
Institution General hospital	3	–6 to 12	0.545
Experience 5–10 years *vs* **<5 years**	2	–11 to 17	0.793
Experience >10 years *vs* **5–10 years**	-2	–16 to 13	0.749
PEDeDose user partly *vs* **no**	-1	–15 to 16	0.913
PEDeDose user yes *vs* **partly**	-6	–20 to 10	0.467
Unadjusted model			
Intervention basic *vs* **control**	–20	–24 to –16	<0.001
Intervention full *vs* **basic**	–31	–35 to –27	<0.001

The table shows the results of the exploratory analyses comparing the CDSS PEDeDose (full) with the structured PEDeDose dosing information and a pocket calculator (basic), and basic with the SmPC and a pocket calculator (control). The multivariable and unadjusted models with only the intervention variable and random intercepts for both subject and item are presented. The reference category of the comparisons is marked in bold.
CDSS, clinical decision support system; SmPC, Summary of Product Characteristics.

Table 4 Assumed error types identified based on the participants' response

Error counts			
Error types	**Control**	**Basic**	**Full**
Total error count	70	49	14
Protocol deviations*	12	5	4
Decimal error	2	3	0
Maximum dose not respected	27	17	0
Daily versus single dose	6	0	0
Wrong information used†	11	11	4
Transcription error	N/A	N/A	1
Wrong CDSS user entry/selection	N/A	N/A	4
Unknown	16	13	1

Column values exceed the total error count when multiple error types were identified. The categories correspond to the CDSS PEDeDose (full), PEDeDose dosing information with a pocket calculator (basic) and the SmPC with a pocket calculator (control).
*For example, dosage was not converted to the dispensing unit.
†For example, the loading dose was used instead of the maintenance dose.
CDSS, clinical decision support system; N/A, error type not possible or not identifiable for this intervention; SmPC, Summary of Product Characteristics.

Finally, maximal model specification including by-subject and by-item random intercepts and slopes whenever possible allowed the model to be more flexible in parameter estimation and thus limits inflation of type I error.[24]

Interpretation

The CDSS PEDeDose significantly improved the error rate as compared with the SmPC by reducing the odds of an error by a factor of 12. Furthermore, the CDSS PEDeDose significantly reduced the time needed for the dose derivation by 45%. The effect remained significant when estimating the unadjusted effect of the intervention, thus giving us strong confidence in our results. The sensitivity analysis did not indicate an effect of the intervention order on the number of errors. Even more so, the adjusted analysis suggested that the covariates (ie, fixed effects) had a negligible impact on both outcomes. In contrast, there was high variability between participants and items, (ie, random effects) leading to broad CIs, especially in the two blocks using pocket calculator. However, the variability was drastically reduced when the CDSS PEDeDose is used. This demonstrates that the CDSS PEDeDose was able to mitigate the uncertainty produced by the human factor, while other factors such as experience do not suffice. Thus, the CDSS PEDeDose increased the overall safety of the individually calculated dosages in our simulation. Furthermore, since there were no noteworthy differences between frequent PEDeDose users, infrequent users and new users, we could demonstrate that the usability of the CDSS PEDeDose is excellent.

Our exploratory analyses revealed that the structuring of the dosing information did not substantially improve the error rate, but only the time needed. Although our study was not powered to detect these differences, it was still interesting to see that the differences between PEDeDose with pocket calculator and the CDSS PEDeDose was still striking with fivefold lower odds for an error and 31% reduction of time when using the CDSS.

We were surprised by the high number of errors in the SmPC block (27 of the 70 errors) where the maximum dosage was not respected. Thus, we would like to highlight the example of the drug isoniazid, where the SmPC states the maximum daily dose even multiple times. This error type occurred also frequently when only the structured dosing information was used (17 of 49 errors), even though the maximum dosage is highlighted in a dedicated field. None of this type of error occurred while the participants were using the CDSS PEDeDose as the built-in calculator does respect the maximum dose. This again highlights the importance of providing HCPs with individualised dosing recommendations as repeatedly stating the maximum daily dosage obviously does not suffice and might even be conceptually similar to the pitfalls of over-alerting.[26] Analysis of the PEDeDose logging data revealed that most of the errors committed with the CDSS PEDeDose could be prevented with a reasonable integration into the prescribing software, such as wrong birthdate entries or transcription errors.

Generalisability

Based on the strong results and the inevitability of human errors, we are confident that the use of the CDSS PEDeDose will generally enhance the safety of prescribed dosages in practice. Furthermore, the time reduction that is achieved with the use of the CDSS PEDeDose might be further enhanced in clinical practice. Especially, for off-label prescriptions where additional resources need to be consulted. Overall, it must be noted that our study measured the isolated effect of the web application of the CDSS PEDeDose. This is in contrast to real-world studies where the magnitude of the measured effect will be modified by the way the CDSS is integrated into a primary software (ie, a clinical information system), CDSS uptake (ie, percentage of CDSS use),[27] vigilant HCPs[11 28] or by other measures implemented to prevent such types of errors. These factors might influence the effect in different ways. A bad integration of the CDSS in a clinical information system will compromise usability, uptake and can enable additional types of errors to occur. On the other hand, a good integration will simply rule out even more types of errors by design (eg, transcription errors). Interestingly, clinical information system providers do not need to conduct usability tests as compared with European medical device manufacturers.[29 30] Last but not least, we think that it is undisputable that we should prevent the occurrence of an error in the first place by using a dose calculator rather than to rely on post hoc measures or on the commendable vigilance of the HCPs.[10 11 28]

Comparison with literature

Even though there are a multitude of dosing calculators freely available, surprisingly, almost all lack a conformité européenne (CE) marking.[31] Furthermore, there are only few contemporary studies that assess dose prescribing errors in a simulation.[19 32 33] Siebert *et al* found significant error reduction with the use of a mobile app during drug preparation in paediatric emergency settings.[32 33] Interestingly, the baseline error rates in both studies were strikingly high with values of 63%[33] and 75%[32] as compared with the 23% in our study. However, comparison is limited as they did not assess the dose calculation step in isolation. Thus, we want to highlight the most similar study by van der Zanden *et al* that assessed the former website-integrated dosing calculator of the Dutch Paediatric Formulary.[19 34] However, the calculator is not available anymore. They found 26% and 17% clinically relevant errors in the manual group and in the calculator group, respectively. This resulted in a non-significant estimated mean difference of 7% in favour of the calculator group. However, they used a between-subject design and a 2 min time limit per item. We think that the use of a within-subject instead of a between-subject design was a major strength in our study. Furthermore, we did not impose a time limit, as otherwise we could not estimate the time needed for the dose derivation. A time limit probably would have increased the manual error rate even further, but the results would be influenced by the participants' reading speed.

CONCLUSION AND OUTLOOK

We demonstrated that the CDSS PEDeDose with its built-in calculator significantly reduced the error rate and time needed for the dose derivation for paediatric patients and neonates when compared with the SmPC in a simulation trial. The high variability in error rates within HCPs could be mitigated when PEDeDose was used. Interestingly, no substantial improvement of structured (basic) versus full-text (control) dosing information was found. Our simulation showed that by limiting the human factor and by providing guidance during the dose derivation step, dose calculation errors can be reduced. A reasonable integration of the CDSS into the electronic workflow of paediatric prescribing may even further limit the human factor during the prescribing step, and thus could prevent additional error types by design.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants but the study did not fall within the scope of the Swiss human research act. This was clarified in advance with the responsible ethics comitee exempted this study. Participants gave informed consent to participate in the study before taking part.

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