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Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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Title

Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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Abstract

Background

Drug dosing errors are among the most frequent causes of preventable harm in pediatrics. Due to the complexity of pediatric 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. HCP 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 randomized 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 HCP participated in the trial. The odds ratio for an erroneous dosage using the CDSS as compared to the SmPC with pocket calculator was 0.08 (95% CI 0.02 to 0.36, $p < .001$). Thus, the odds of an error were 12-times higher while using the SmPC. Furthermore, there was a 45% (95% CI 39% to 51%, $p < .001$) 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 pediatrics. 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.

Introduction

Background and objectives

In pediatric 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 pediatric populations and are prescribed off-label.[2,3] Additionally, developmental changes affecting the pharmacokinetics have to be considered when prescribing.[4] As a consequence, pediatric 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 pediatric 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 pediatric pharmacotherapy.[12]

PEDeDose is a CDSS to facilitate drug dosing in pediatrics.[13,14] It provides health care professionals (HCP) 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. A comprehensive description of PEDeDose has been published previously.[13]

We hypothesized 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 to manual calculation using a pocket calculator. To assess this, a randomized within-subject simulation trial was conducted, where HCPs were asked to calculate dosages for hypothetical but clinically relevant patient cases.

Methods

Trial design

We conducted a randomized 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 pediatric patient, was created (Supplement 1). The items were developed by the main author (LH) and reviewed by two clinical pharmacists (KK, PV) with extensive experience in the field of pediatrics and neonatology. Only drugs with a pediatric 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 visualized in Figure 1.

No ethical approval was necessary as the study did not fall within the scope of the Swiss Human Research Act. This was clarified in advance with the responsible ethics commission. We report this study in concordance with the 'Reporting Guidelines for Health Care 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 pediatric clinics, and HCPs working in the ambulatory setting i.e. 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 consented to the data collection and received a small monetary compensation for their participation.

Interventions

The CDSS PEDeDose encompasses a database with general pediatric dosing information and a built-in calculator for individualized 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 can be viewed as a semi-structured electronic resource, that is written

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3 in plain text, while the data of the PEDeDose database is highly structured. Thus, to isolate the effect
4 of structuring drug dosing information, we exploratorily assessed the impact of using PEDeDose
5 without the built-in calculator. An example of the structured dosing information from PEDeDose is
6 shown in Supplement 2.
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10 **Simulation setup**

11 The trial was developed using the Gorilla Experiment Builder (www.gorilla.sc), a web-based trial
12 platform.[18] We conducted the trial at the participants workplace. Depending on the availability
13 participants were using their own computers or were provided with a notebook for the trial. The Gorilla
14 website was opened in a browser while the interventions (i.e. SmPC or PEDeDose websites) were
15 opened either in a different browser tab or window, depending on the participants preferences. Before
16 the trial started, every participant was briefed about the aim and the design of the trial. Subsequently,
17 the participants were required to solve a dedicated test example with the PEDeDose built-in calculator
18 (*full*). This ensured that the participants fully understood the capabilities of PEDeDose, such as the
19 possibility to convert the calculated dosage to the correct dosing unit (e.g. mg to mL).
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28 Participants were instructed to round the calculated dosage to a maximum of two decimal places. If a
29 dose range was provided by the respective dosing information, participants were asked to submit a
30 range as a result, too.
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34 **Outcomes**

35 The primary outcome was the correctness of the derived dosage, a binary variable with 1 = error and
36 0 = correct. The secondary outcome was the time needed to solve an item.
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40 Since the dosing information that the participants were required to use was specified in advance and
41 no additional clinical evaluation was required, there was an objectively correct dosage for every item
42 within the corresponding dosing information (SmPC or PEDeDose). Errors were defined as submitted
43 responses that exceeded clinically non-relevant deviations of 5% or 10% for drugs with narrow or wide
44 therapeutic windows, respectively (Supplement 1). Even though the participants were required to
45 submit dose ranges as a range, we did not consider it an error if the submitted dosage was a single
46 dosage that was within the correct window. We reviewed all erroneous responses and tried to
47 determine the possible cause of error. For the errors that were found in the *full* block (i.e. PEDeDose
48 with built-in calculator), the logging data of the PEDeDose built-in calculator were additionally
49 analyzed. This allowed us to assess whether the participant had specified the calculator inputs
50 incorrectly (i.e. drug, indication, route of administration, birthdate, weight, height, and gestational
51 age).
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3 The secondary outcome response time was defined as the time difference (in seconds) for each item
4 between the time stamp on the mouse click that initialized item loading and the click that submitted
5 the result. We defined outliers in the time outcome as values greater than three standard deviations
6 for each intervention. We removed outliers and missing values and analyzed only complete items.
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10 **Covariates**

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

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

40 Randomization was done on the level of the interventions and the items (Figure 1). Thus, for each
41 participant the order of the three interventions was randomized, while for each intervention six out of
42 the pool of 18 items were randomly drawn without replacement. The Gorilla Experimental Builder
43 enabled to design the randomization procedure directly into the trial, thus taking care of the
44 participant allocation.[18]
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50 **Statistical methods**

51 Statistical analyses were performed in R version 4.1.1.[20] The relevant functions and additional
52 packages used are denoted as *function* {package}. The only continuous variable was the secondary
53 outcome response time per item, which was transformed using the natural logarithm to achieve
54 normality of the residuals. Orthogonal sum-to-zero contrasts for the unordered factors 'institution'
55 and 'profession' applying *contr.sum* {stats} were used. The lower-level effects were thus estimated at
56 the level of the grand mean and interpreted accordingly. We applied difference coding for the ordered
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3 factors 'experience', 'PEDeDose user', and the exploratory version of the variable 'intervention' using
4 *contr.sdif* {MASS}.[21] Thus, each level of the ordered factors was compared to their previous level.
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6 The contrast coding scheme is provided in the supplement (Supplement 4).
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9 For the primary outcome 'error', we fitted a generalized linear mixed-effects model (GLMM) with a
10 logit-link function using *glmer* {lme4}.[22] The secondary outcome 'time' was assessed by fitting a
11 linear mixed-effects model (LMM) using *lmer* {lmerTest}.[23] All models were derived by starting with
12 maximal model specification based on the trial design, and then sequentially reducing model
13 complexity until a non-singular fit was achieved.[24] We started by defining by-subject and by-item
14 random intercepts and slopes (i.e. crossed-random effects) on each type of intervention. The main
15 variable 'intervention' and the additional covariates were treated as fixed variables.
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21 In exploratory analyses, we assessed the impact of structuring the dosing information by adding the
22 intervention *basic* (i.e. PEDeDose without the built-in calculator). Thus, the binary variable for the
23 intervention became an ordered three-level factor (*control, basic, full*). As a sensitivity analysis we
24 created a model that is only adjusted for the order of the interventions.
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28 For all models also an unadjusted model was built, containing only the variable 'intervention' as well
29 as only random intercepts for both subject and item, respectively. We derived Wald confidence
30 intervals. The *p*-values for the linear models were derived via Satterthwaite's degrees of freedom
31 method.[23] The estimated marginal means for the 'intervention' variable for all the models were
32 calculated using *emmeans* {emmeans}.[25] The summary outputs of the models are reported in the
33 supplement (Supplement 4).
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Results

Participants

In total, 53 HCPs participated in the study. 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 randomization order are visualized in Figure 2.

The characteristics of the participants are summarized in Table 1.

Table 1: Participant characteristics

Variable names	Number (%)
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)

Recruitment

The participants were mainly recruited via convenience sampling by directly contacting the responsible head of department in Swiss children's hospitals, general hospitals with pediatric clinics, or by the company's newsletter. Furthermore, snowball sampling was used as many of the participating HCPs were also helping recruiting their colleagues. The recruitment period ranged from January to July 2022.

Missing values and outliers

Of the total 936 items rated, there were four responses (0.4%) classified as missing, three in the *full* intervention, which were accidentally skipped and one 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 analyzed, 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 analyzed

Overall, 932 items were analyzed 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 analyzed, 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 (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 generalized linear mixed-effects model with a logit-link was defined to estimate the adjusted odds ratio for dose derivation errors. The regression formula for the generalized linear mixed-effects model is shown below in R notation (I). The model included the covariates for institution and previous PDeDose 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) $error \sim intervention + institution + user (intervention | subject) + (intervention | item)$

(II) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 2: Results of the confirmatory multivariable analyses and the unadjusted models with only the intervention variable and random intercepts for both subject and item.

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			
Intervention full vs control	0.08	0.02 to 0.36	<.001
Institution Children's hospital	1.27	0.75 to 2.15	.382
Institution General hospital	1.12	0.74 to 1.70	.587
PEDeDose user partly vs no	0.57	0.27 to 1.29	.178
PEDeDose user yes vs partly	0.88	0.37 to 2.11	.771
Unadjusted model			
Intervention full vs control	0.15	0.08 to 0.27	<.001
Time			
	Time change (%)	95% Confidence interval	p-value
Multivariable model			
Intervention full vs control	-45	-51 to -39	<.001
Institution Children's hospital	-18	-26 to -8	<.001
Institution General hospital	3	-6 to 12	.585
Experience (5-10 y vs <5 y)	3	-11 to 18	.722
Experience >10 y vs 5-10 y	1	-16 to 15	.862
PEDeDose user partly vs no	6	-9 to 26	.472
PEDeDose user yes vs partly	-8	-22 to 9	.357

Unadjusted model			
Intervention Full vs control	-45	-48 to -42	<.001

Ancillary analyses

Exploratory analyses

Additionally, we explored the impact of using structured dosing information while using a pocket calculator. The model formula of the generalized 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 to 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 (Supplement 4).

(III) $error \sim intervention + institution + user + (1 | subject) + (1 | item)$

(IV) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 3: Results of the exploratory multivariable analyses and the unadjusted models with only the intervention variable and random intercepts for both subject and item.

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			
Intervention basic vs control	0.67	0.44 to 1.03	.068
Intervention full vs basic	0.22	0.12 to 0.42	<.001
Institution Children's hospital	1.37	0.9 to 2.08	.143
Institution General hospital	0.97	0.68 to 1.38	.860
Experience 5-10 y vs <5 y	1.36	0.79 to 2.36	.273

Experience >10 y vs 5-10 y	1.15	0.64 to 2.05	.644
PEDeDose user partly vs no	0.51	0.26 to 1.00	.050
PEDeDose user yes vs partly	1.33	0.68 to 2.62	.402
Unadjusted model			
Intervention basic vs control	0.67	0.44 to 1.02	.063
Intervention Full vs basic	0.22	0.12 to 0.41	<.001
Time			
	Time change (%)	95% Confidence interval	p-value
Multivariable model			
Intervention basic vs control	-20	-27 to -12	<.001
Intervention full vs basic	-31	-38 to -23	<.001
Institution Children's hospital	-18	-26 to -10	<.001
Institution General hospital	3	-6 to 12	.545
Experience 5-10 y vs <5 y	2	-11 to 17	.793
Experience >10 y vs 5-10 y	-2	-16 to 13	.749
PEDeDose user partly vs no	-1	-15 to 16	.913
PEDeDose user yes vs partly	-6	-20 to 10	.467
Unadjusted model			
Intervention basic vs control	-20	-24 to -16	<.001
Intervention	-31	-35 to -27	<.001

full vs basic			
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Analysis of error types

We determined the assumed reason for each error that occurred. The logging data of the PEdDose 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.

Table 4: Assumed error types identified based on the participants' response. Column values exceed the total error count when multiple error types were identified.

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 vs 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

N/A = error type not possible or not identifiable for this intervention.

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 to either the structured PEDeDose dosing information (*basic*) or the semi-structured 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. Randomization 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 (e.g. 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 (e.g. 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 pediatric label could be created. In pediatric 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. 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 to 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 (i.e. fixed effects) had a negligible impact on both outcomes. In contrast, there was high variability between participants and items, (i.e. random effects) leading to broad confidence intervals, especially in the two blocks using pocket calculator. However, the variability was drastically reduced when the CDSS PEDeDose is used. This demonstrates that the

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3 CDSS PEdDose was able to mitigate the uncertainty produced by the human factor, while other
4 factors such as experience do not suffice. Thus, the CDSS PEdDose increased the overall safety of the
5 individually calculated dosages in our simulation. Furthermore, since there were no noteworthy
6 differences between frequent PEdDose users, infrequent users, and new users, we could
7 demonstrate that the usability of the CDSS PEdDose is excellent.
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12 Our exploratory analyses revealed that the structuring of the dosing information did not substantially
13 improve the error rate, but only the time needed. Although our study was not powered to detect these
14 differences, it was still interesting to see that the differences between PEdDose with pocket
15 calculator and the CDSS PEdDose was still striking with five-fold lower odds for an error and 31%
16 reduction of time when using the CDSS.
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21 The error types that were assumed to be the reason for an incorrect result should be interpreted
22 cautiously. They are strongly depending on the item itself and only limited information can be
23 extracted from the participants' response. For example, not every active ingredient has a loading and
24 maintenance dose that may be confused. We were surprised by the high number of errors in the SmPC
25 block (27 of the 70 errors) where the maximum dosage was not respected. Thus, we would like to
26 highlight the example of the drug isoniazid, where the SmPC states the maximum daily dose even
27 multiple times. This error type occurred also frequently when only the structured dosing information
28 was used (17 of 49 errors), even though the maximum dosage is highlighted in a dedicated field. None
29 of this type of error occurred while the participants were using the CDSS PEdDose as the built-in
30 calculator does respect the maximum dose. This again highlights the importance of providing HCPs
31 with individualized dosing recommendations as repeatedly stating the maximum daily dosage
32 obviously does not suffice and might even be conceptually similar to the pitfalls of over-alerting.[26]
33 Analysis of the PEdDose logging data revealed that most of the errors committed with the CDSS
34 PEdDose could be prevented with a reasonable integration into the prescribing software, such as
35 wrong birthdate entries or transcription errors.
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47 **Generalizability**

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

17 **Comparison with literature**

19 Even though there are a multitude of dosing calculators freely available, surprisingly, almost all lack a
20 *conformité européenne* (CE) marking.[31] Furthermore, there are only few contemporary studies that
21 assess dose prescribing errors in a simulation.[19,32,33] Siebert and colleagues found significant error
22 reduction with the use of a mobile app during drug preparation in pediatric emergency
23 settings.[32,33]. Interestingly, the baseline error rates in both studies were strikingly high with values
24 of 63% [33] and 75% [32] as compared to the 23% in our study. However, comparison is limited as they
25 did not assess the dose calculation step in isolation. Thus, we want to highlight the most similar study
26 by van der Zanden *et al.* that assessed the former website-integrated dosing calculator of the Dutch
27 Pediatric Formulary.[19,34] However, the calculator is not available anymore. They found 26% and
28 17% clinically relevant errors in the manual group and in the calculator group, respectively. This
29 resulted in a non-significant estimated mean difference of 7% in favor of the calculator group.
30 However, they used a between-subject design and a two-minute time limit per item. We think that the
31 use of a within-subject instead of a between-subject design was a major strength in our study.
32 Furthermore, we did not impose a time limit, as otherwise we could not estimate the time needed for
33 the dose derivation. A time limit probably would have increased the manual error rate even further,
34 but the results would be influenced by the participants' reading speed.

47 **Conclusion and outlook**

48 We demonstrated that the CDSS PEDeDose with its built-in calculator significantly reduced the error
49 rate and time needed for the dose derivation for pediatric patients and neonates when compared to
50 the SmPC in a simulation trial. The high variability in error rates within HCPs could be mitigated when
51 PEDeDose was used. Interestingly, no substantial improvement of structured *versus* semi-structured
52 dosing information was found. This shows us that by limiting the human factor and by providing
53 guidance during the dose derivation step, dosing errors can be significantly reduced or may even
54 completely be eliminated by design. A reasonable integration of the CDSS into the electronic workflow
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3 of pediatric prescribing may even further limit the human factor during the prescribing step, and thus
4 could prevent additional error types by design.
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Other information

Data availability

The data and the R scripts for the statistical analysis are provided in the supplements 5, 6, and 7.

Conflicts of interest

LH as a PhD student is funded by PEDeus Ltd. LH, KK, MW and PV are employees of PEDeus Ltd. MG is a member of the board of directors of PEDeus Ltd as well as the medical director of the University Children's Hospital Zurich. None of the authors has any ownership in either institution. The PEDeus Ltd. is a 100% subsidiary company of the University Children's Hospital Zurich. The authors have no additional conflicts of interest to declare that are relevant to the content of this article.

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Figures

Figure 1: Visualization of the trial design. The name of the interventions full, basic, and control correspond to the CDSS PEDeDose with built-in calculator, PEDeDose used together with a pocket calculator, and Summary of Product Characteristics used together with a pocket calculator, respectively.

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 full, basic, and control correspond to the CDSS PEDeDose with built-in calculator, PEDeDose used together with a pocket calculator, and Summary of Product Characteristics with pocket calculator, respectively.

Figure 3: Bar plot depicting the number of errors stratified by the type of intervention. The name of the interventions full, basic, and control correspond to the CDSS PEDeDose with built-in calculator, PEDeDose used together with a pocket calculator, and Summary of Product Characteristics with pocket calculator, respectively.

Figure 4: Violin plot depicting the median time per participant stratified by the type of intervention. Below each plot the overall median [Q1, Q3] of the intervention is shown. The name of the interventions full, basic, and control correspond to CDSS PEDeDose with built-in calculator, PEDeDose used together with a pocket calculator, and Summary of Product Characteristics with pocket calculator, respectively.

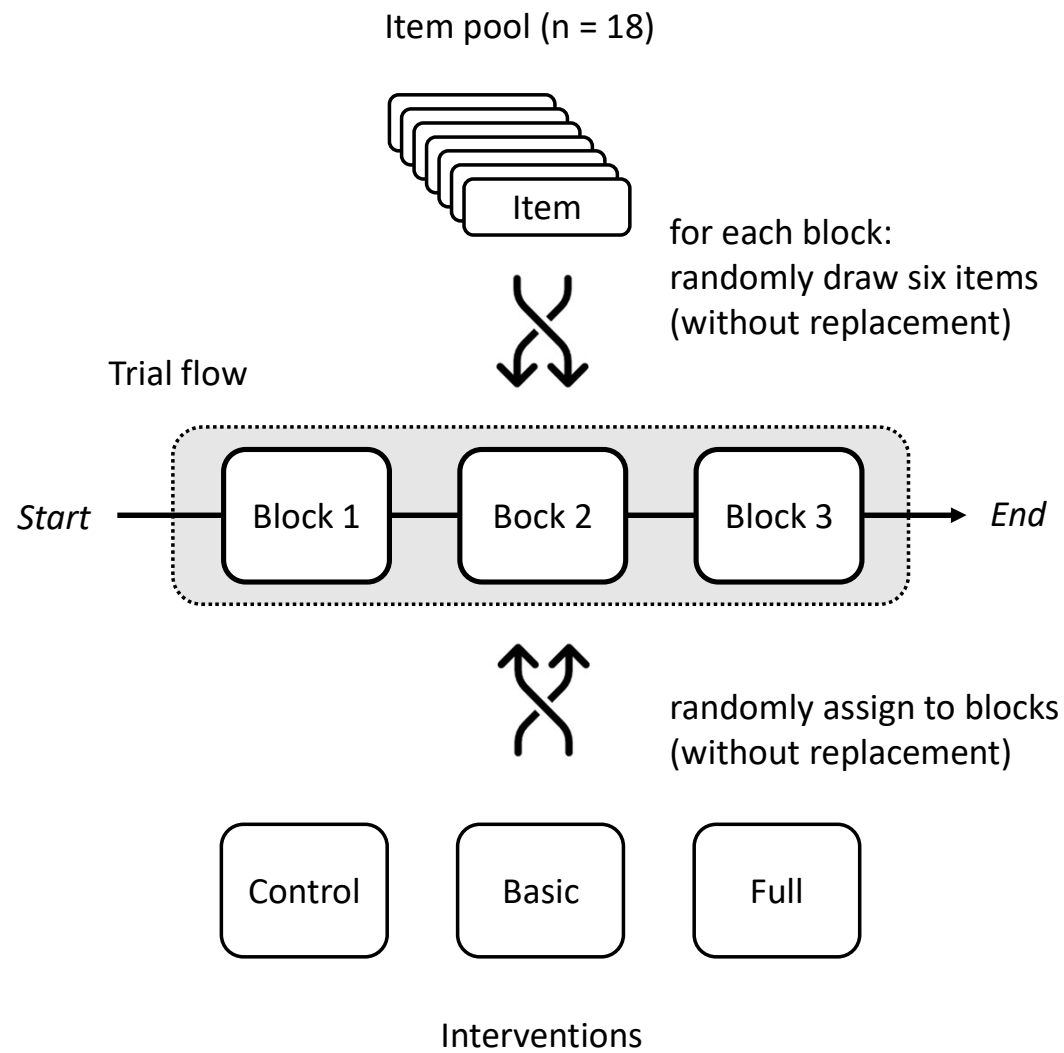
Figure 5: Number of errors stratified by intervention order and type. The name of the interventions full, basic, and control correspond to the CDSS PEDeDose with built-in calculator, PEDeDose used together with a pocket calculator, and Summary of Product Characteristics with pocket calculator, respectively.

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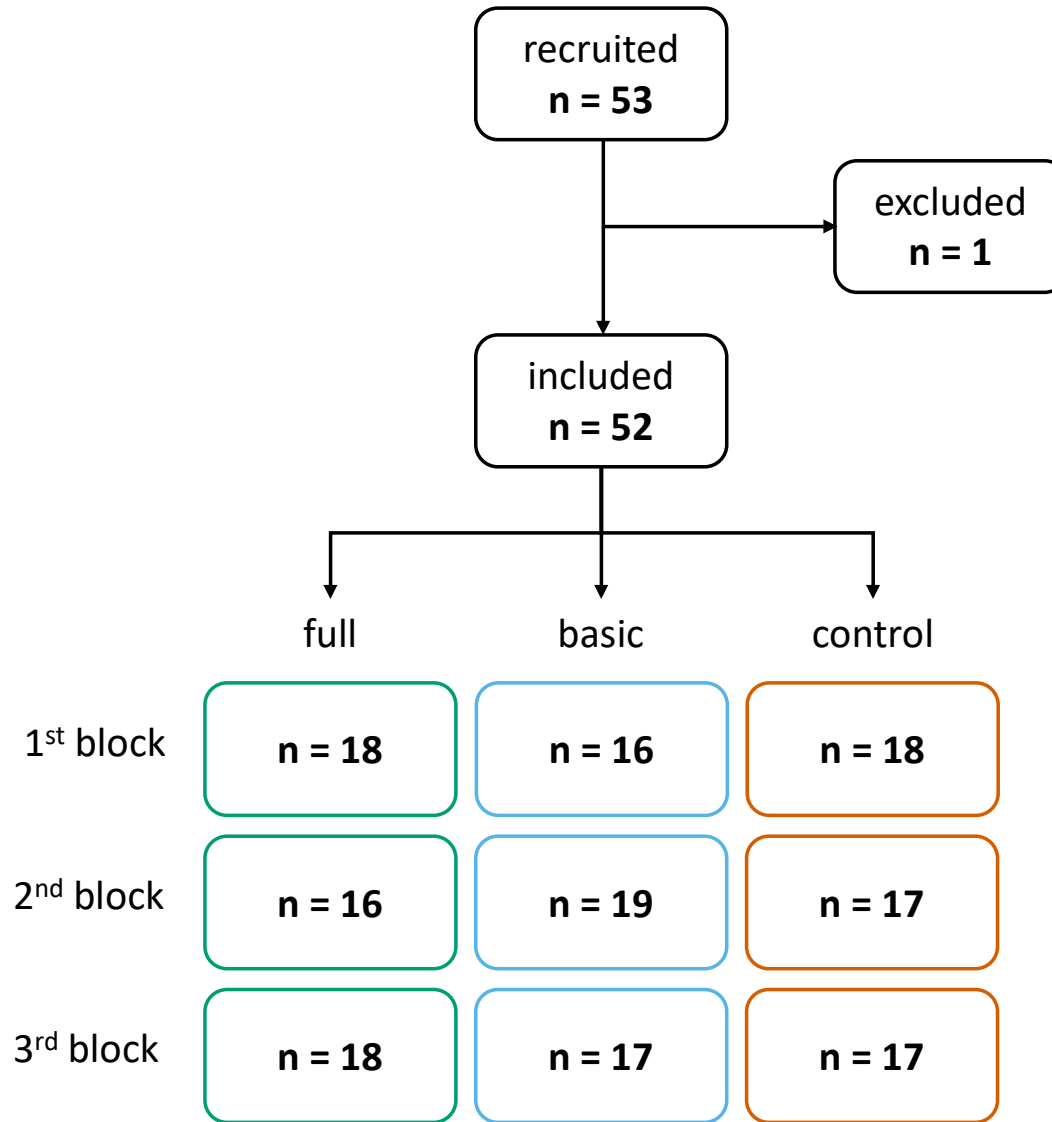
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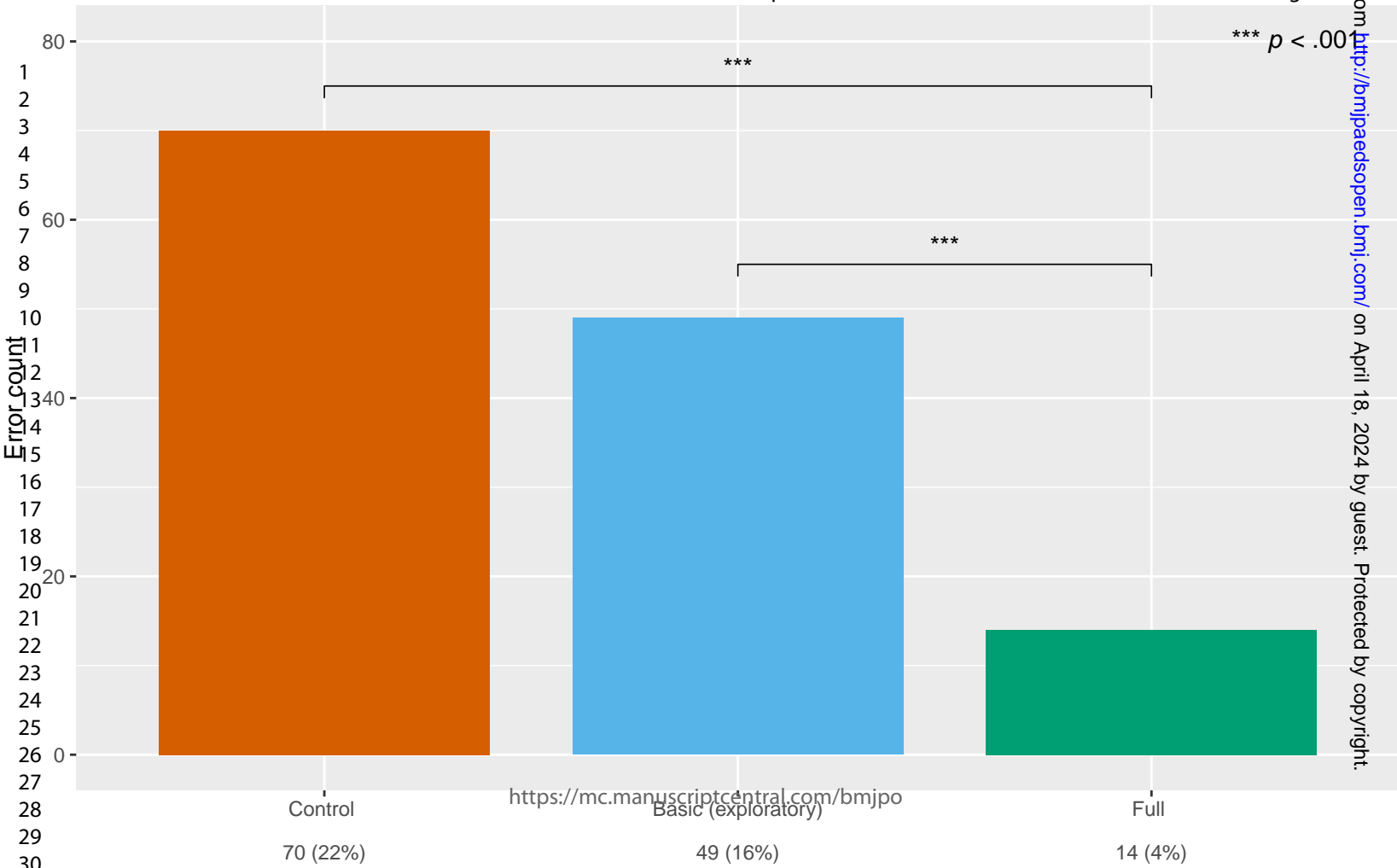


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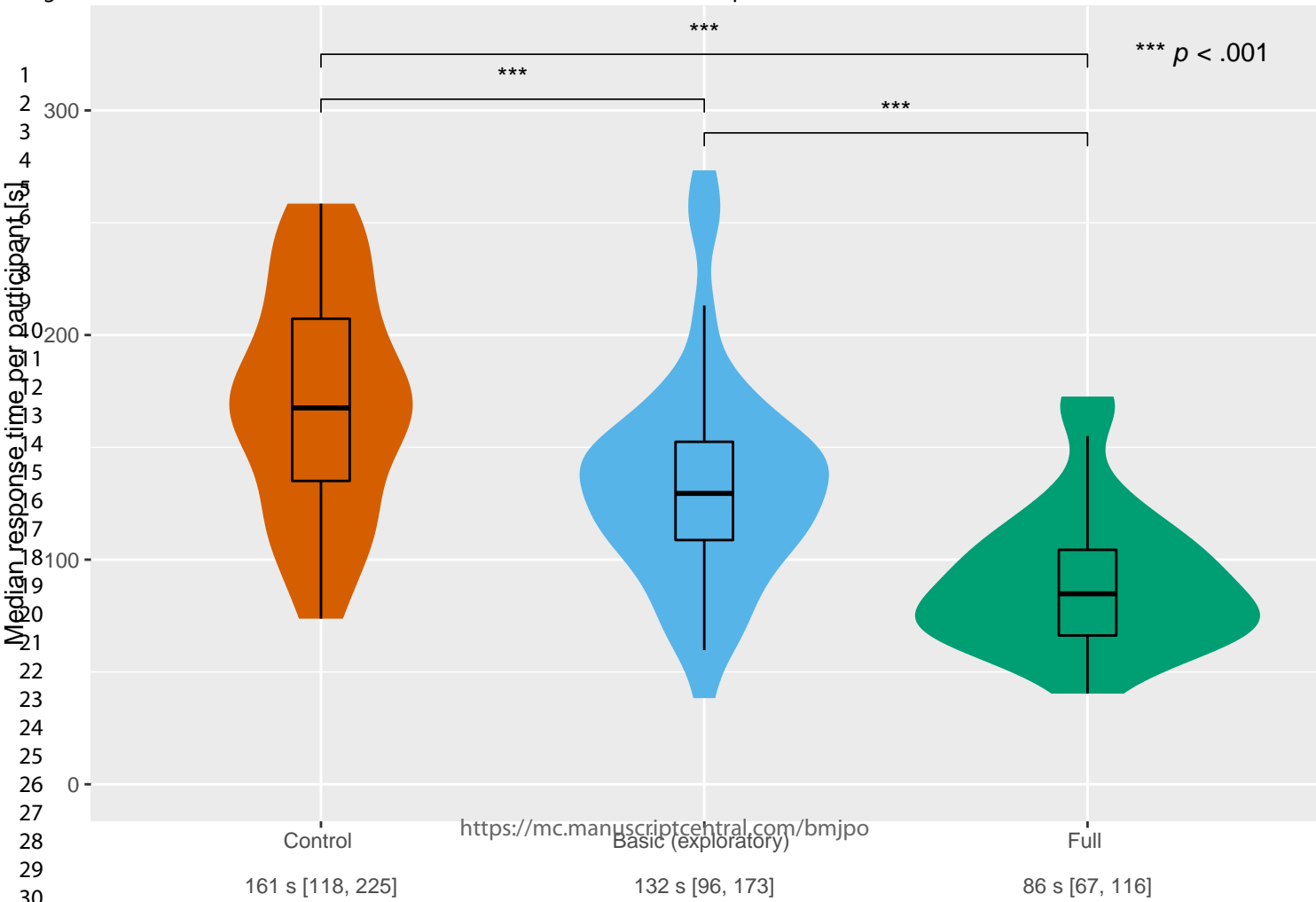


Number of errors stratified by intervention



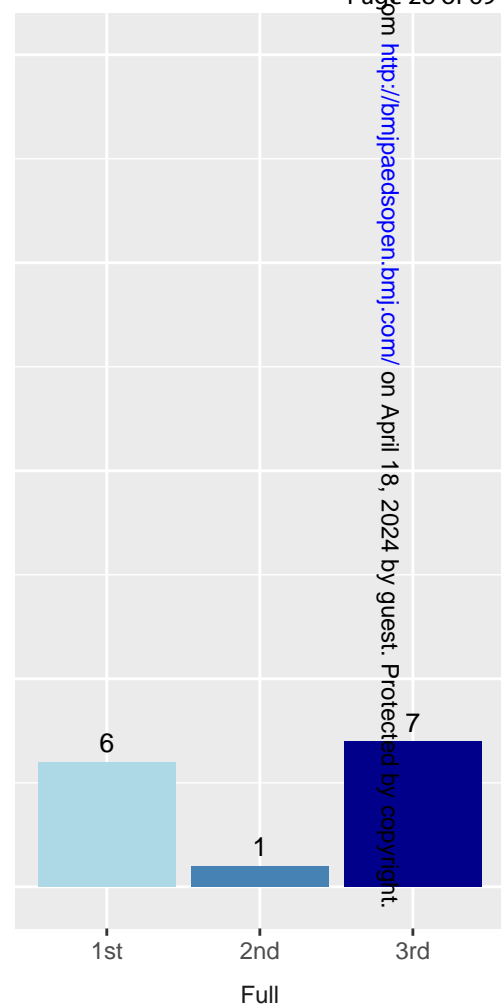
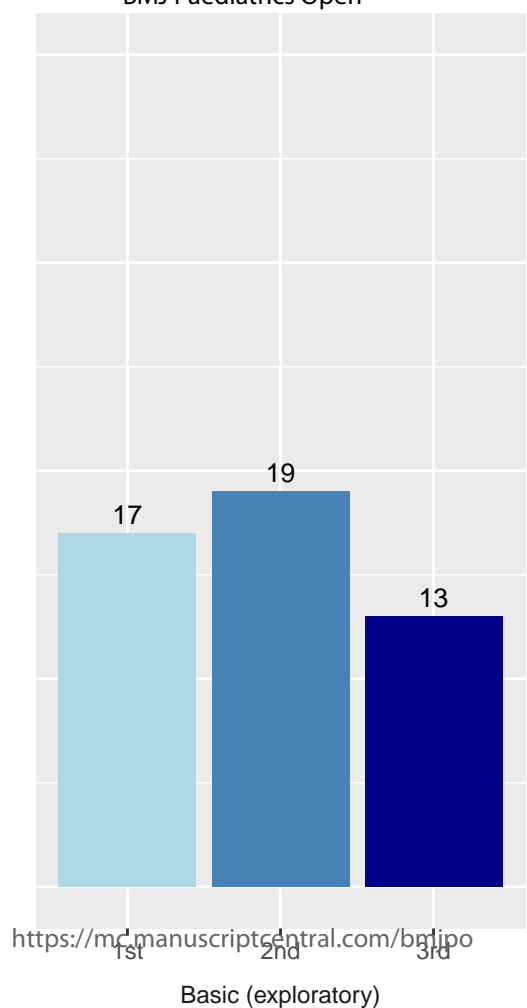
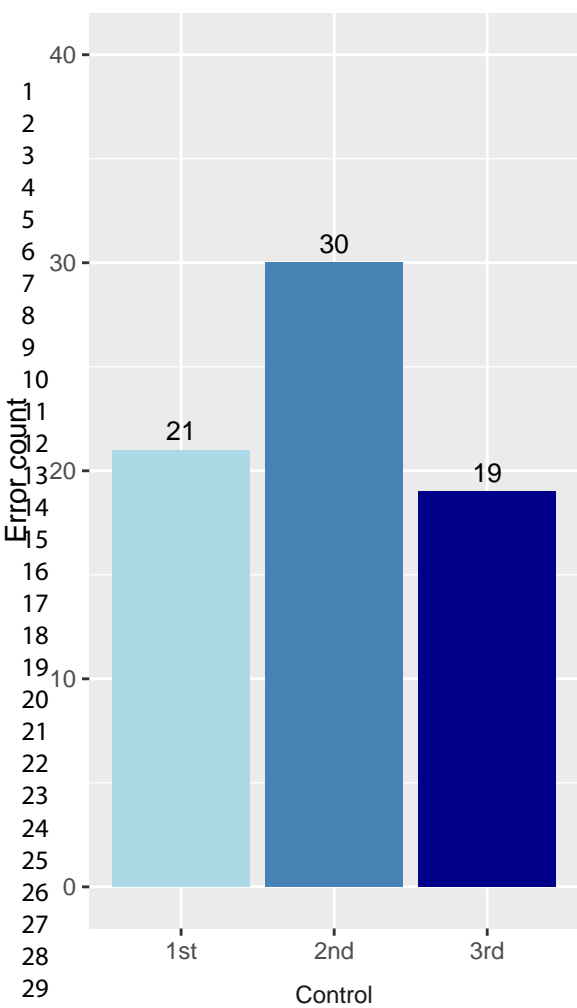
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Median response time per participant stratified by intervention



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Number of errors stratified by intervention and by order



Supplement 1 – Description of items

ID	Dosing unit	Indication	Drug product	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
1	mL/dose	infection in cystic fibrosis patients	Ciproxin Suspension 5 g/100 mL	p.o. (liquid)	-	2x daily	6y 10mth	26	-	no
2	mg/dose	bacterial infection (severe)	Vancomycin Sandoz i.v. 500 mg	i.v.	-	4x daily	5wks ^d	4.18	-	yes – GA 35 2/7
3	drops/dose	epilepsy	Rivotril Tropfen ^b	p.o. (liquid)	loading dose / begin	3x daily	6y 7mth	29	-	no
4	mL/dose	acute otitis media	Co-Amoxi-Mepha Suspension 457	p.o. (liquid)	-	2x daily	2y 8mth	14	-	no
5	mL/dose	candidiasis (systemic)	Diflucan forte Suspension 200 mg/5 mL	p.o. (liquid)	-	1x daily	8y	31	-	no
6	mg/dose	bacterial infection (severe)	Floxapen 500 mg	i.v.	-	3x daily	6d	3.2	-	no

ID	Dispensing unit	Indication	Drug product	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
7	mg/dose	nausea and vomiting in chemotherapy	Mephameson Injektionslösung 4 mg/mL	i.v.	-	4x daily	1y 6mth	12	81	no
8	mg/dose	arthritis	Metoject ^b 10 mg/0.2 ml	s.c.	-	1x weekly	12y 5mth	36	138	no
9	mL/dose	prophylaxis of acute rejection in patients with allogenic kidney transplantation (in combination with ciclosporin and corticosteroids)	Cellcept Suspension ^b 200 mg/mL	p.o. (liquid)	-	2x daily	9y 3mth	32	122	no
10	mg/dose	fungal infection (invasive)	Caspofungin Sandoz eco i.v. 70 mg	i.v.	loading dose / begin	-	11mth	9.5	76	no
11	mL/dose	bacterial infection	Klacided Kindersuspension 125 mg/5 mL	p.o. (liquid)	-	2x daily	7mth	7.6	-	no
12	mg/dose	tuberculosis	Isoniazid Labatec	p.o.	-	1x daily	10y 7mth	38	-	no

ID	Dispensing unit	Indication	Drug product	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
13	mL/dose	nausea and vomiting in chemotherapy	Zofran Sirup 4 mg/5 mL	p.o. (liquid)	follow-up treatment	3x daily	14y 10mth	46	BSA ^c : >1.2 m ²	no
14	mg/dose	bacterial infection	Rocephin	i.m.	-	1x daily	5wks ^d	3.82	-	yes – GA 36 5/7
15	mL/dose	pruritus	Atarax Sirup 2 mg/mL	p.o. (liquid)	-	3x daily	5y 4mth	24	-	no
16	mg/dose	intoxication with benzodiazepines	Anexate	i.v.	loading dose / begin	-	8y 6mth	36	-	no
17	mL/dose	insomnia	Nervifene Lösung	p.o. (liquid)	-	1x daily	5y 1mth	22	-	no
18	mg/dose	urolithiasis (urates / urinary stones)	Zyloric 100 mg	p.o.	-	1x daily	13y 1mth	42	-	no

^a Age was shown to participants as birthdate calculated on the day of the experiment

^b Substance with narrow therapeutic window

^c BSA = body surface area (for this item the BSA was provided for the SmPC user as the dosing information differentiated between BSA >1.2 m² or <1.2 m²)

^d corrected age

Supplement 2 – Example of the structured dosing information of PEdeDose

Substance		Vancomycin									
Indication		bacterial infection, severe									
Route of administration		IV, parenteral									
Calculated dose											
Age	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
5 wk	4.18 kg		IV		63 mg/dose	4 x daily			by inf	B	
Date of birth 03.08.2022		Weight 4.18 kg	PI Yes	GA 35 2/7 WOP	corrA 5 wk	PNA 10 wk					
You must enter the height to be able to calculate the BMI.											
Products in Switzerland matching the data set of the calculated dose											
General doses											
Age/PMA	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
< 30 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 24 h after the loading dose; by inf	D	
< 30 wk		PI	IV	maintenance	20 mg/kg/dose	1 x daily			first maintenance dose 24 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 18 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	maintenance	20 mg/kg/dose	every 18 h			first maintenance dose 18 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 12 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	maintenance	20 mg/kg/dose	2 x daily			first maintenance dose 12 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	(A)	
28 D - 18 Y and < 66 kg			IV		15 mg/kg/dose	4 x daily			by inf	B	
< 18 Y and ≥ 66 kg			IV		1000 mg/dose	4 x daily			by inf	B	

Figure: Example of the vancomycin dosage information for severe bacterial infection to be administered intravenously. In the calculated dosage tab one can see the calculated dosage for a hypothetical preterm of 5 weeks of age (corrected age) with a weight of 4.18 kg analogous to item number 2 of the trial. In the general doses tab the basic dosing information can be seen.

Supplement 3 – Sample size estimation

Expected power for significant improvement of the CDSS PEDeDose vs no CDSS

Error rate without CDSS: 20%

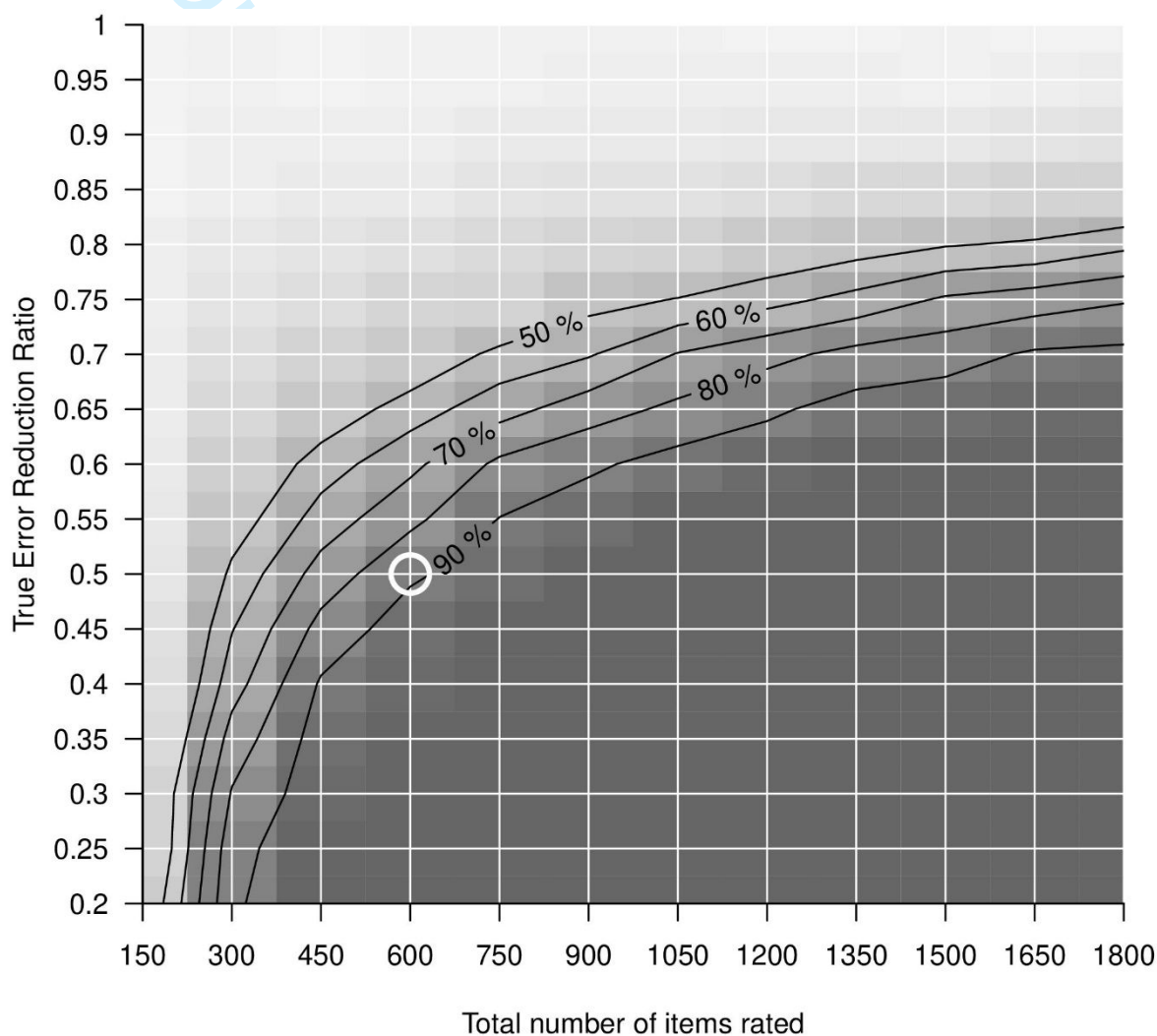


Figure: The experiment was simulated 999 times assuming between 150 to 1800 items that are rated, while achieving an error reduction ratio between 0.2 to 1 (no reduction). The white circle marks the estimated number of items that need to be rated to achieve a 50% error reduction.

Supplement 4 - Statistical analyses

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Confirmatory analysis

Errors (full model)

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention	0.08	0.02	0.36	<0.001
Institution (Children's hospital)	1.27	0.75	2.15	0.3823
Institution (Hospital)	1.12	0.74	1.70	0.5875
User (partly vs no)	0.57	0.26	1.29	0.1779
User (yes vs partly)	0.88	0.37	2.11	0.7712

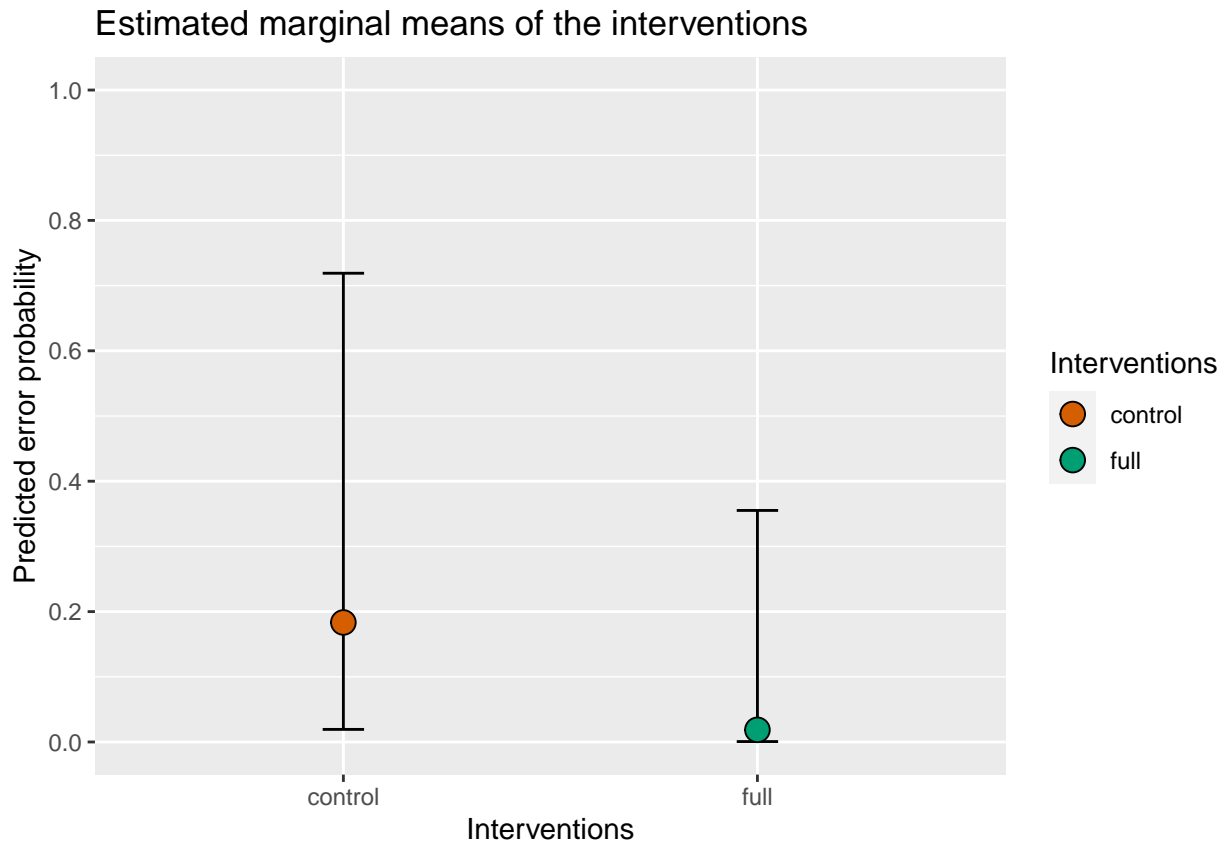
R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula:
## error ~ intervention + institution + user + (intervention | subject) +
## (intervention | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##  457.2   510.4  -216.6   433.2     608
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8811 -0.4334 -0.2101 -0.1185  3.7005
##
## Random effects:
##  Groups Name          Variance Std.Dev. Corr
##  subject (Intercept)  0.2340  0.4838
##           interventionfull 1.4835  1.2180 -0.51
##  item   (Intercept)  0.2954  0.5435
##           interventionfull 0.7559  0.8694 -0.35
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)   -1.4938    0.2415  -6.187 6.15e-10 ***
## interventionfull -2.4694    0.7395  -3.339 0.000839 ***
## institution1     0.2359    0.2700   0.874 0.382263
## institution2     0.1151    0.2121   0.543 0.587464
## userpartly-no   -0.5563    0.4129  -1.347 0.177867
## useryes-partly  -0.1302    0.4478  -0.291 0.771219
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
```

```

##          (Intr) intrvn instt1 instt2 usrpr-
## intrvntnfl1 -0.252
## institutin1 -0.139 -0.091
## institutin2 -0.137  0.034 -0.404
## userprtly-n  0.238  0.040 -0.297  0.165
## usry-sprtly -0.129  0.144 -0.390  0.164 -0.467
    
```

Plot - Predicted probability of error



www Only

Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention	0.15	0.08	0.27	<0.001

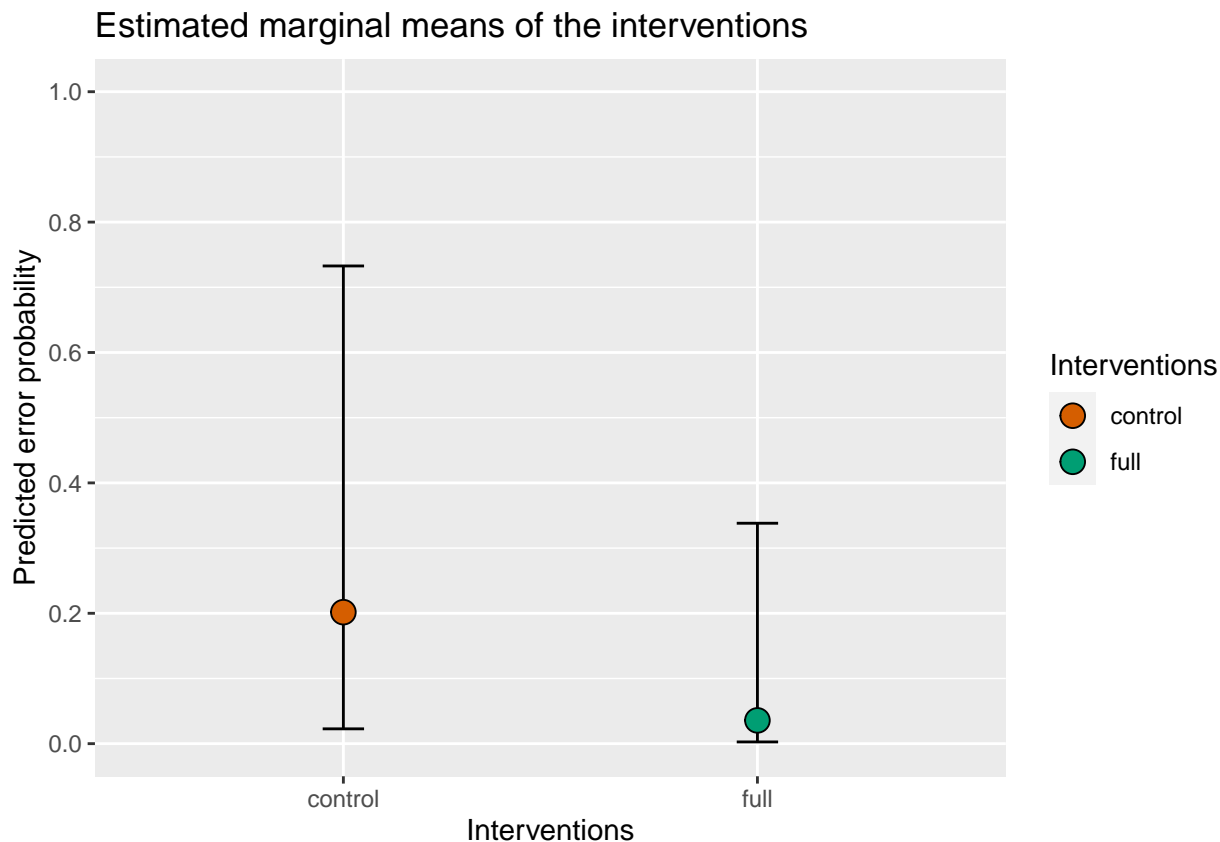
R summary output

```

## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##           AIC      BIC   logLik deviance df.resid
##      447.0    464.8  -219.5   439.0     616
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8104 -0.4473 -0.2367 -0.1683  5.8528
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2236   0.4728
##  item (Intercept)    0.2925   0.5408
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -1.3756    0.2165  -6.355 2.09e-10 ***
## interventionfull -1.9200    0.3183  -6.032 1.62e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.242

```

Plot - Predicted probability of error



Review Only

Time (full model)

Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-44.85	-50.51	-38.54	<0.001
Institution (Children's hospital)	-17.78	-26.16	-8.46	<0.001
Institution (Hospital)	2.60	-6.37	12.42	0.5853
Experience (5-10y vs <5y)	2.64	-10.99	18.36	0.7217
Experience (>10y vs 5-10y)	-1.39	-15.75	15.40	0.8619
User (partly vs no)	6.34	-9.92	25.52	0.4717
User (yes vs partly)	-7.73	-22.11	9.30	0.3568

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_confirmatory
##
## REML criterion at convergence: 432.7
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -3.4708 -0.6145 -0.0595  0.5344  3.1635
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject (Intercept)          0.04406  0.2099
##           interventionfull 0.05292  0.2300  -0.35
##   item     (Intercept)          0.06619  0.2573
##           interventionfull 0.02677  0.1636  -0.91
## Residual                    0.08039  0.2835
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    5.12111    0.07072 26.21325  72.415 < 2e-16 ***
## interventionfull -0.59507    0.05524 30.37710 -10.773 6.74e-12 ***
## institution1    -0.19580    0.05480 44.96048  -3.573 0.000856 ***
## institution2     0.02564    0.04665 44.84160   0.550 0.585265
## experience5-10y-<5y  0.02606    0.07269 44.77178   0.359 0.721652
## experience>10y-5-10y -0.01404    0.08025 44.96372  -0.175 0.861888
## userpartly-no     0.06144    0.08463 44.84683   0.726 0.471654
## useryes-partly    -0.08049    0.08645 45.06018  -0.931 0.356777
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##           (Intr) intrvn instt1 instt2 e5-10- e>10-5 usrpr-
```

Time (full model)

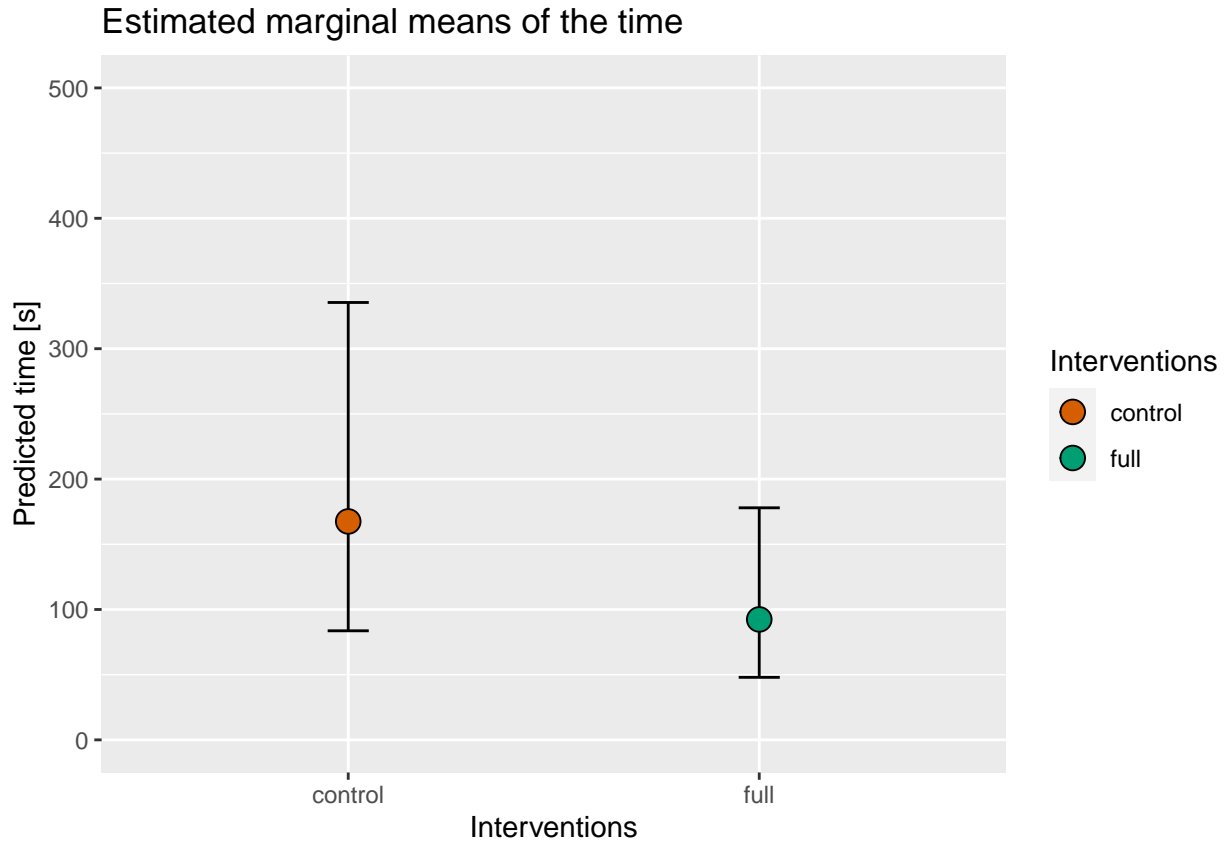
CONFIRMATORY ANALYSIS

```

1
2
3  ## intrvntnfl1 -0.698
4  ## institutin1 -0.071 -0.001
5  ## institutin2 -0.064 0.000 -0.412
6  ## expr5-10-<5 0.039 -0.002 -0.027 -0.311
7  ## exp>10-5-10 0.062 0.000 0.159 0.035 -0.442
8  ## userprtly-n 0.114 0.002 -0.292 0.199 -0.043 -0.047
9  ## usrys-prtly -0.073 -0.001 -0.375 0.134 0.000 0.007 -0.466
10
11
12

```

Plot - Predicted response time



Only

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Time (simple model)

Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-45	-47.73	-42.12	<0.001

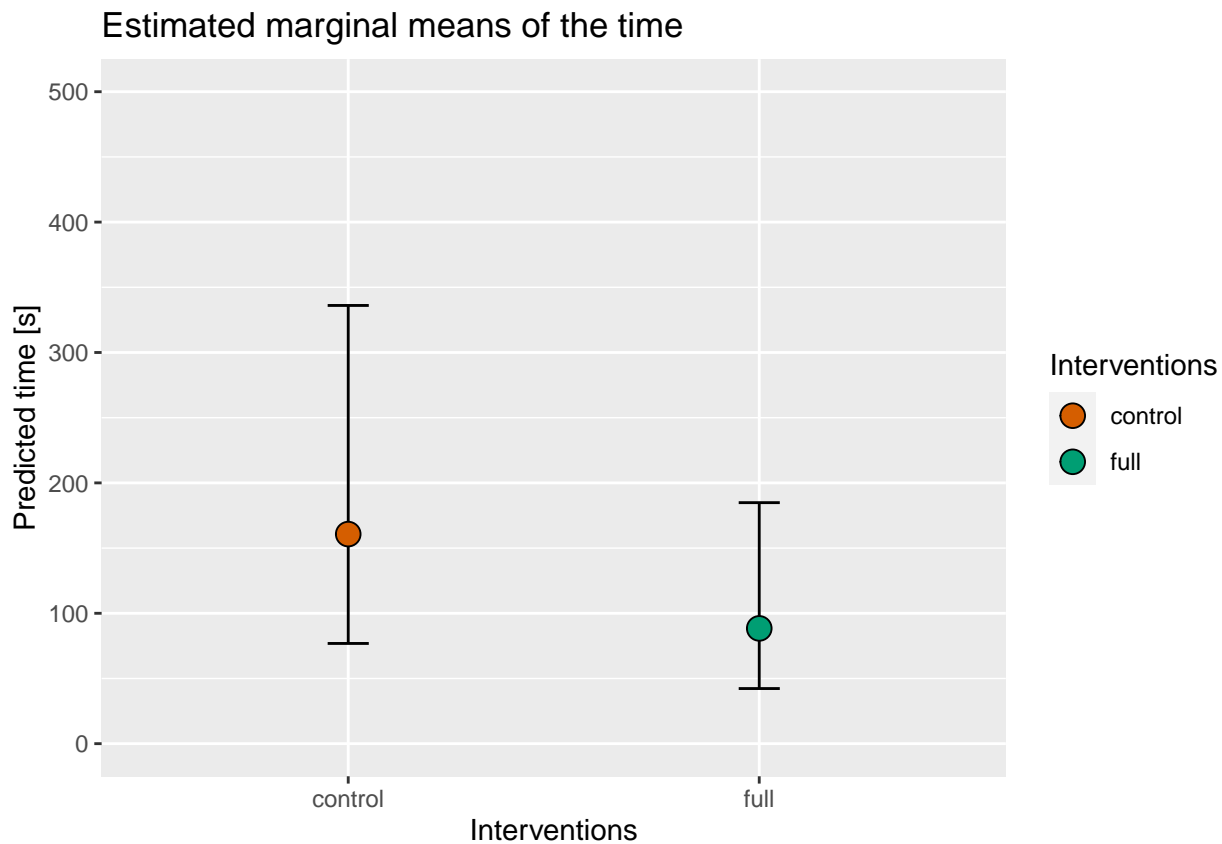
R summary output

```

## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
##
## REML criterion at convergence: 494.8
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -4.0767 -0.6149 -0.0248  0.5679  3.3763
##
## Random effects:
##   Groups   Name                Variance Std.Dev.
## subject  (Intercept)  0.05797  0.2408
## item     (Intercept)  0.03607  0.1899
## Residual                    0.10085  0.3176
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    5.07975    0.05877 38.59148   86.44 <2e-16 ***
## interventionfull -0.59777    0.02604 551.44043  -22.95 <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.222

```

Plot - Predicted response time



Review Only

Exploratory analysis

Errors (full model)

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0677
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Institution (Children's hospital)	1.37	0.90	2.08	0.1428
Institution (Hospital)	0.97	0.68	1.38	0.8601
Experience (5-10y vs <5y)	1.36	0.79	2.36	0.2725
Experience (>10y vs 5-10y)	1.15	0.64	2.05	0.6443
User (partly vs no)	0.51	0.26	1.00	0.0498
User (yes vs partly)	1.33	0.68	2.62	0.4019

R summary output

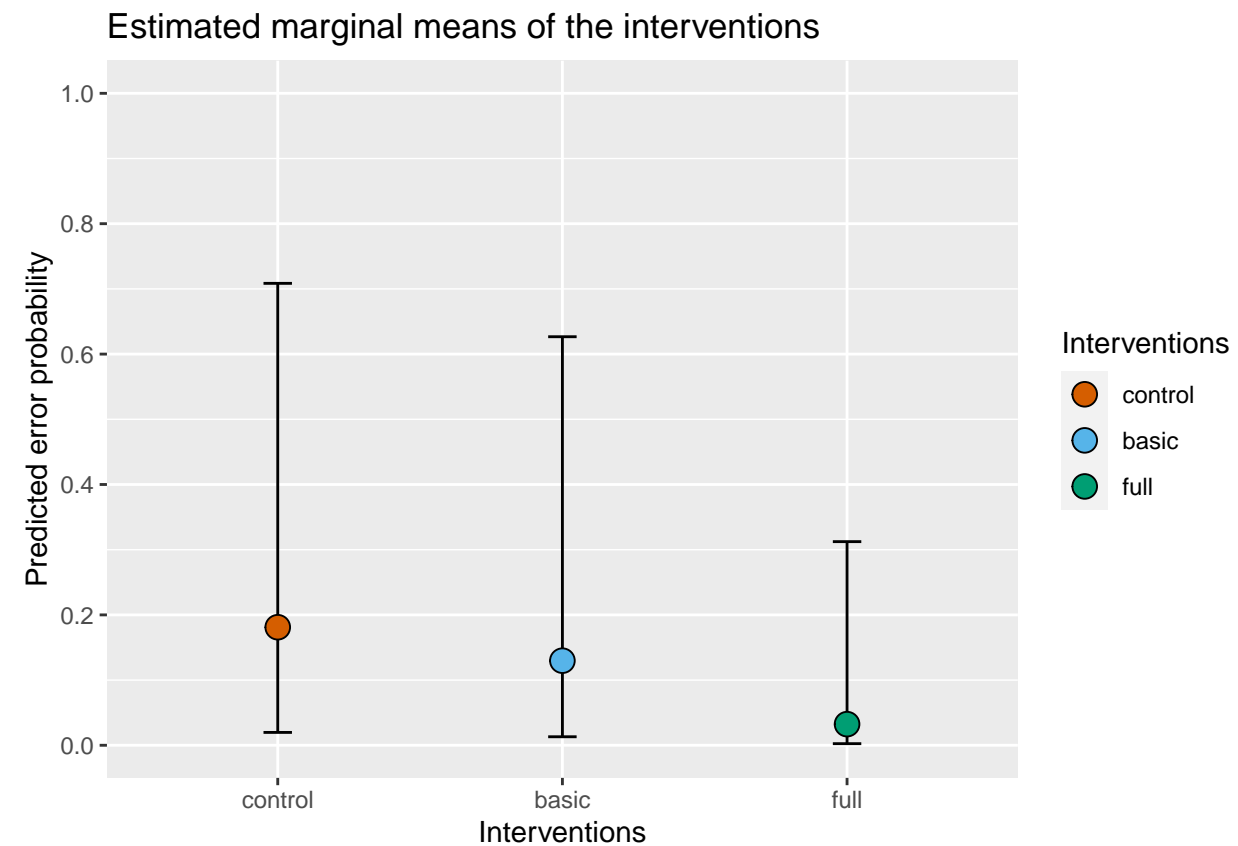
```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + institution + experience + user + (1 |
## subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##    711.6    764.9   -344.8   689.6     921
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0078 -0.4323 -0.2991 -0.1736  6.2086
##
## Random effects:
##  Groups Name          Variance Std.Dev.
##  subject (Intercept) 0.1555    0.3943
##  item    (Intercept) 0.3354    0.5791
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -2.26943    0.21046 -10.783 < 2e-16 ***
## interventionbasic-control -0.39394    0.21565  -1.827  0.0677 .
## interventionfull-basic   -1.49297    0.31775  -4.699 2.62e-06 ***
## institution1             0.31265    0.21334   1.466  0.1428
## institution2            -0.03148    0.17857  -0.176  0.8601
## experience5-10y-<5y      0.30767    0.28040   1.097  0.2725
## experience>10y-5-10y    0.13731    0.29742   0.462  0.6443
## userpartly-no           -0.67513    0.34415  -1.962  0.0498 *
## useryes-partly          0.28866    0.34439   0.838  0.4019
## ---
```

```

1  ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
2  ##
3  ## Correlation of Fixed Effects:
4  ##
5  ##      (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
6  ## intrvntnbs-  0.043
7  ## intrvntnfl-  0.277 -0.374
8  ## institutin1 -0.173 -0.002   -0.010
9  ## institutin2 -0.098 -0.006   -0.005   -0.345
10 ## expr5-10-<5  0.019  0.000   -0.010   -0.042 -0.314
11 ## exp>10-5-10  0.061 -0.004    0.005    0.146  0.070 -0.431
12 ## userprtly-n  0.239  0.007    0.007   -0.312  0.178 -0.039 -0.037
13 ## usry-sprtly -0.137 -0.009    0.002   -0.324  0.113  0.023  0.025 -0.529
14
15
16

```

Plot - Predicted probability of error



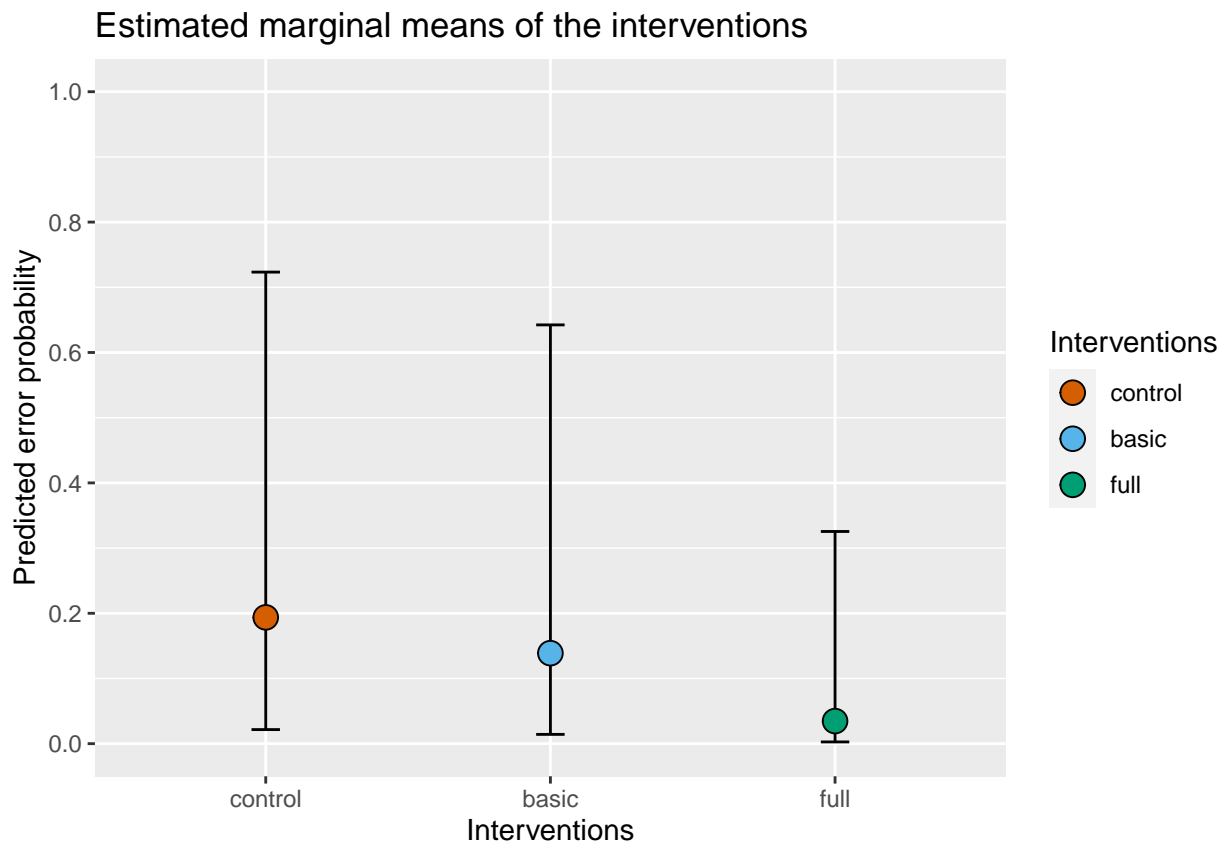
Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.02	0.0629
Intervention (full vs basic)	0.22	0.12	0.41	<0.001

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##    706.8    731.0   -348.4    696.8     927
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.9847 -0.4297 -0.3089 -0.1722  5.7553
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2545   0.5044
##  item    (Intercept) 0.3500   0.5916
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1927    0.2047 -10.710 < 2e-16 ***
## interventionbasic-control -0.3994    0.2148  -1.860  0.0629 .
## interventionfull-basic  -1.5014    0.3169  -4.738 2.16e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.044
## intrvntnfl-  0.282 -0.375
```

Plot - Predicted probability of error



Review Only

Time (full model)

Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.95	-27.14	-12.06	<0.001
Intervention (full vs basic)	-30.99	-38.42	-22.67	<0.001
Institution (Children's hospital)	-18.44	-26.38	-9.64	<0.001
Institution (Hospital)	2.75	-5.83	12.12	0.5453
Experience (5-10y vs <5y)	1.85	-11.10	16.69	0.7926
Experience (>10y vs 5-10y)	-2.43	-16.02	13.36	0.7493
User (partly vs no)	-0.88	-15.39	16.12	0.9133
User (yes vs partly)	-5.87	-19.92	10.63	0.4666

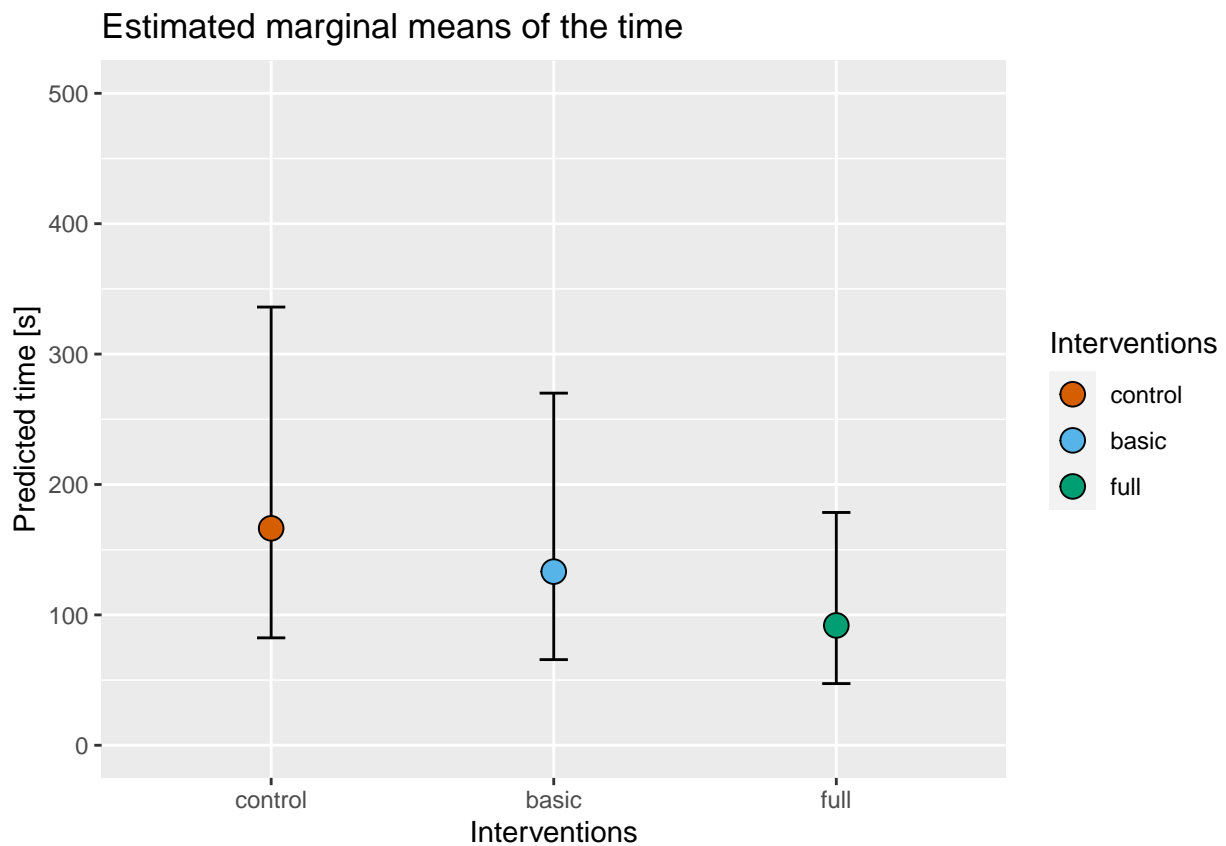
R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_exploratory
##
## REML criterion at convergence: 653.6
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -4.1903 -0.5998 -0.0537  0.5331  3.2470
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject (Intercept)          0.03751  0.1937
##           interventionbasic-control 0.03513  0.1874  0.10
##           interventionfull-basic    0.06151  0.2480  0.02 -0.47
##   item    (Intercept)          0.04184  0.2045
##           interventionbasic-control 0.01928  0.1388  0.01
##           interventionfull-basic    0.02960  0.1721 -0.76 -0.48
## Residual                    0.08292  0.2880
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    4.842339   0.057639 30.008155  84.011 < 2e-16 ***
## interventionbasic-control -0.222575   0.048001 28.046824  -4.637 7.46e-05 ***
## interventionfull-basic   -0.370936   0.058103 30.941660  -6.384 4.17e-07 ***
## institution1    -0.203848   0.052280 44.997416  -3.899 0.000319 ***
## institution2     0.027128   0.044511 44.920751   0.609 0.545288
## experience5-10y-<5y    0.018346   0.069372 44.871124   0.264 0.792633
## experience>10y-5-10y -0.024608   0.076541 44.953549  -0.321 0.749324
## userpartly-no    -0.008842   0.080746 44.900724  -0.110 0.913292
## useryes-partly   -0.060522   0.082432 45.008740  -0.734 0.466626
## ---
```

```

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##          (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
## intrvntnbs-  0.030
## intrvntnfl- -0.439 -0.476
## institutin1 -0.083  0.001   -0.001
## institutin2 -0.075  0.000    0.000   -0.412
## expr5-10-<5  0.045 -0.001    0.000   -0.028  -0.312
## exp>10-5-10  0.073  0.000    0.000    0.158  0.035 -0.442
## userprtly-n  0.134  0.001    0.001   -0.292  0.200 -0.043 -0.046
## usry-sprtly -0.086 -0.002    0.001   -0.374  0.134  0.001  0.007 -0.467
    
```

Plot - Predicted response time



Time (simple model)

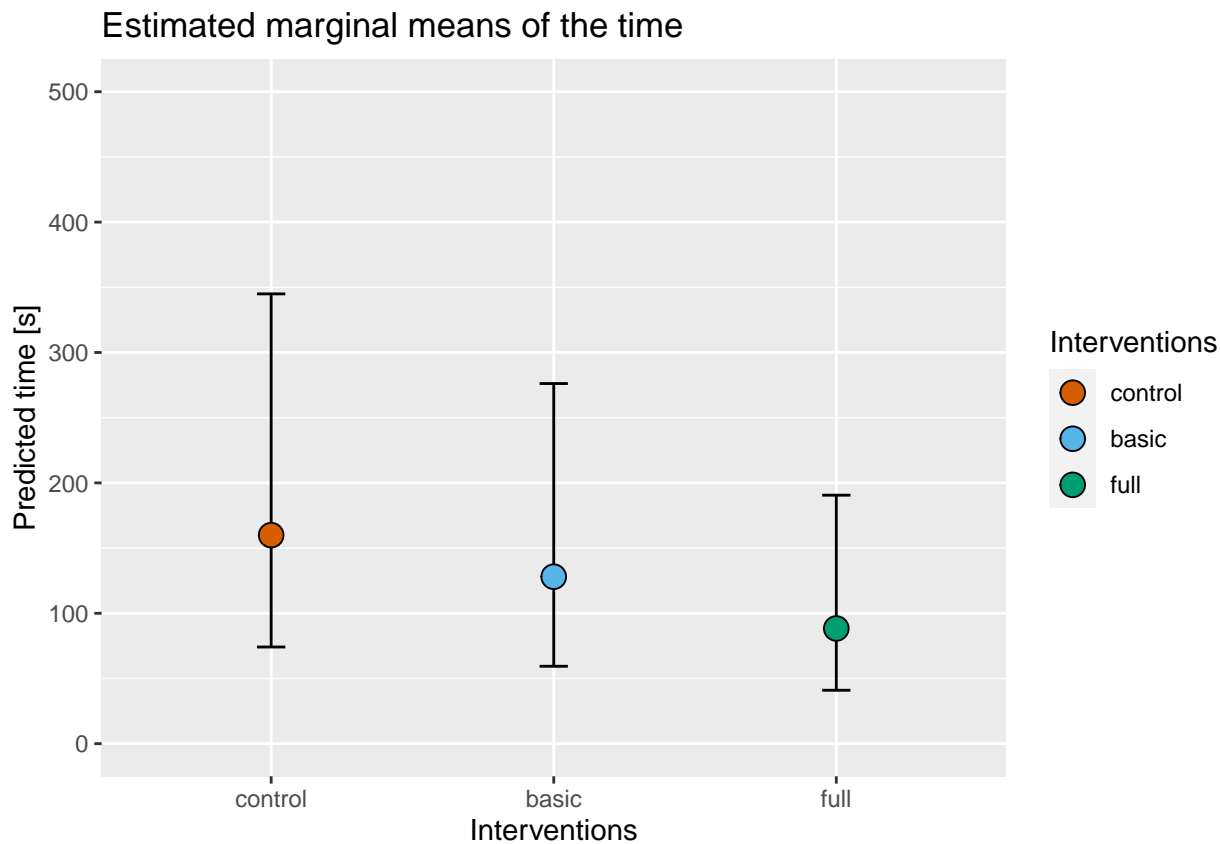
Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.93	-24.01	-15.62	<0.001
Intervention (full vs basic)	-31.01	-34.51	-27.32	<0.001

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
##
## REML criterion at convergence: 762.6
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -3.7745 -0.6461 -0.0532  0.6139  3.7661
##
## Random effects:
##   Groups Name          Variance Std.Dev.
##   subject (Intercept) 0.06287  0.2507
##   item    (Intercept) 0.04405  0.2099
##   Residual                0.10814  0.3288
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error   df t value Pr(>|t|)
## (Intercept)      4.80288    0.06142 33.80208  78.194 < 2e-16 ***
## interventionbasic-control -0.22223    0.02671 861.13236  -8.319 3.45e-16 ***
## interventionfull-basic   -0.37118    0.02660 860.23224 -13.953 < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.000
## intrvntnfl-  0.001 -0.495
```

Plot - Predicted response time



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Sensitivity analysis

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0664
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Order (block 2 vs block 1)	1.14	0.71	1.83	0.5822
Order (block 3 vs block 1)	0.80	0.49	1.32	0.3783

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + block_order + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC    logLik deviance df.resid
##    708.8    742.7   -347.4    694.8     925
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0778 -0.4245 -0.3108 -0.1725  6.5485
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2403   0.4902
##  item    (Intercept) 0.3724   0.6102
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1675    0.2493  -8.693 < 2e-16 ***
## interventionbasic-control -0.3950    0.2152  -1.835  0.0664 .
## interventionfull-basic  -1.4935    0.3173  -4.707 2.51e-06 ***
## block_order2         0.1327    0.2412   0.550  0.5822
## block_order3        -0.2238    0.2541  -0.881  0.3783
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb- intrvntnf- blk_2
## intrvntnbs-   0.049
## intrvntnfl-   0.212 -0.376
## block_ordr2  -0.497 -0.022    0.031
## block_ordr3  -0.466 -0.024    0.023    0.494
```

Contrasts

Contrast matrices for categorical variables

Intervention (exploratory)

```
##          basic-control full-basic
## control  -0.6666667 -0.3333333
## basic    0.3333333 -0.3333333
## full     0.3333333  0.6666667
```

User

```
##          partly-no yes-partly
## no      -0.6666667 -0.3333333
## partly  0.3333333 -0.3333333
## yes     0.3333333  0.6666667
```

Experience

```
##          5-10y-<5y >10y-5-10y
## <5y      -0.6666667 -0.3333333
## 5-10y    0.3333333 -0.3333333
## >10y     0.3333333  0.6666667
```

Institution

```
##          [,1] [,2]
## Children's hospital  1  0
## Hospital             0  1
## Community            -1 -1
```

1
2
3 subject;"item";"intervention";"intervention_order";"institution";"profession";"experience";"user";"time";"log
4 1;"1";"control";"2";"Childrens hospital";"Physician";"5-10y";"yes";299.11;5.70081139871125;0
5 1;"2";"full";"1";"Childrens hospital";"Physician";"5-10y";"yes";142.95;4.96249491876832;0
6 1;"3";"basic";"3";"Childrens hospital";"Physician";"5-10y";"yes";365.89;5.90233274178014;0
7 1;"4";"control";"2";"Childrens hospital";"Physician";"5-10y";"yes";272.3;5.60690439967971;1
8 1;"5";"full";"1";"Childrens hospital";"Physician";"5-10y";"yes";94.01;4.54340115959046;0
9 1;"6";"basic";"3";"Childrens hospital";"Physician";"5-10y";"yes";105.11;4.65500742083526;0
10 1;"7";"full";"1";"Childrens hospital";"Physician";"5-10y";"yes";NA;NA;0
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34 52;"9";"full";"2";"Community";"Pharmacist";"<5y";"no";142.08;4.95639027924386;0
35 52;"10";"basic";"1";"Community";"Pharmacist";"<5y";"no";263.16;5.5727622122178;0
36 52;"11";"full";"2";"Community";"Pharmacist";"<5y";"no";89.12;4.48998377617897;0
37 52;"12";"control";"3";"Community";"Pharmacist";"<5y";"no";113.37;4.73065680602951;0
38 52;"13";"full";"2";"Community";"Pharmacist";"<5y";"no";90.7;4.50755735712109;0
39 52;"14";"full";"2";"Community";"Pharmacist";"<5y";"no";109.25;4.6936388339757;0
40 52;"15";"full";"2";"Community";"Pharmacist";"<5y";"no";79.21;4.37210255347619;0
41 52;"16";"control";"3";"Community";"Pharmacist";"<5y";"no";157.84;5.06158186171436;0
42 52;"17";"control";"3";"Community";"Pharmacist";"<5y";"no";263.29;5.57325608628995;0
43 52;"18";"basic";"1";"Community";"Pharmacist";"<5y";"no";283.47;5.64710629746264;0
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Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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Title

Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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What is already known on this topic:

Drug dose calculation errors are a well-reported source of preventable harm in pediatrics. CDSS 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 PDeDose, 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 health care providers to use them.

Abstract

Background

Drug dosing errors are among the most frequent causes of preventable harm in pediatrics. Due to the complexity of pediatric 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. HCP 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 randomized 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 HCP participated in the trial. The odds ratio for an erroneous dosage using the CDSS as compared to the SmPC with pocket calculator was 0.08 (95% CI 0.02 to 0.36, $p < .001$). Thus, the odds of an error were 12-times higher while using the SmPC. Furthermore, there was a 45% (95% CI 39% to 51%, $p < .001$) 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 pediatrics. 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.

Introduction

Background and objectives

In pediatric 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 pediatric populations and are prescribed off-label.[2,3] Additionally, developmental changes affecting the pharmacokinetics have to be considered when prescribing.[4] As a consequence, pediatric 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 pediatric 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 pediatric pharmacotherapy.[12]

PEDeDose is a CDSS to facilitate drug dosing in pediatrics.[13,14] It provides health care professionals (HCP) 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. A comprehensive description of PEDeDose and its validation has been published previously.[13]

We hypothesized 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 to manual calculation using a pocket calculator. To assess this, a randomized within-subject simulation trial was conducted, where HCPs were asked to calculate dosages for hypothetical but clinically relevant patient cases.

Methods

Trial design

We conducted a randomized 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 pediatric patient, was created (Supplement 1). The items were developed by the main author (LH) and reviewed by two clinical pharmacists (KK, PV) with extensive experience in the field of pediatrics and neonatology. Only drugs with a pediatric 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 visualized in Figure 1.

No ethical approval was necessary as the study did not fall within the scope of the Swiss Human Research Act. This was clarified in advance with the responsible ethics commission. We report this study in concordance with the 'Reporting Guidelines for Health Care 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 pediatric clinics, and HCPs working in the ambulatory setting i.e. 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 pediatric 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 pediatric dosing information and a built-in calculator for individualized 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

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3 defined three interventions: The Swiss SmPC used together with a pocket calculator (*control*), the CDSS
4 PEdeDose (*full*), and the PEdeDose dosing information used together with a pocket calculator (*basic*).
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6 The study was powered to compare the CDSS PEdeDose (*full*) to the SmPC used together with a pocket
7 calculator (*control*). The SmPC is a full-text electronic resource, while the data of the PEdeDose
8 database is highly structured. Thus, to isolate the effect of structuring drug dosing information, we
9 exploratorily assessed the impact of using PEdeDose without the built-in calculator. An example of the
10 structured dosing information from PEdeDose is shown in Supplement 2.
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15 **Simulation setup**

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17 The trial was developed using the Gorilla Experiment Builder (www.gorilla.sc), a web-based trial
18 platform.[18] We conducted the trial at the participants workplace. Depending on the availability
19 participants were using their own computers or were provided with a notebook for the trial. The Gorilla
20 website was opened in a browser while the interventions (i.e. SmPC or PEdeDose websites) were
21 opened either in a different browser tab or window, depending on the participants preferences. Before
22 the trial started, every participant was briefed about the aim and the design of the trial. Subsequently,
23 the participants were required to solve a dedicated test example with the PEdeDose built-in calculator
24 (*full*). This ensured that the participants fully understood the capabilities of PEdeDose, such as the
25 possibility to convert the calculated dosage to the correct dosing unit (e.g. mg to mL).
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33 Participants were instructed to round the calculated dosage to a maximum of two decimal places. If a
34 dose range was provided by the respective dosing information, participants were asked to submit a
35 range as a result, too.
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39 **Outcomes**

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41 The primary outcome was the correctness of the derived dosage, a binary variable with 1 = error and
42 0 = correct. The secondary outcome was the time needed to solve an item.
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45 Since the dosing information that the participants were required to use was specified in advance and
46 no additional clinical evaluation was required, there was an objectively correct dosage for every item
47 within the corresponding dosing information (SmPC or PEdeDose). Errors were defined as submitted
48 responses that exceeded clinically non-relevant deviations of 5% or 10% for drugs with narrow or wide
49 therapeutic windows, respectively (Supplement 1). Even though the participants were required to
50 submit dose ranges as a range, we did not consider it an error if the submitted dosage was a single
51 dosage that was within the correct window. We reviewed all erroneous responses and tried to
52 determine the possible cause of error. For the errors that were found in the *full* block (i.e. PEdeDose
53 with built-in calculator), the logging data of the PEdeDose built-in calculator were additionally
54 analyzed. This allowed us to assess whether the participant had specified the calculator inputs
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3 incorrectly (i.e. drug, indication, route of administration, birthdate, weight, height, and gestational
4 age).

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7 The secondary outcome response time was defined as the time difference (in seconds) for each item
8 between the time stamp on the mouse click that initialized item loading and the click that submitted
9 the result. We defined outliers in the time outcome as values greater than three standard deviations
10 for each intervention. We removed outliers and missing values and analyzed only complete items.
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13 14 15 **Covariates**

16 The following categorical participant covariates were assessed prior to the trial start: The type of
17 institution where the participant was working as an unordered factor (children's hospital, general
18 hospital with children's clinic, public pharmacy or doctor's office), their profession (physician,
19 pharmacist), their working experience as an ordered factor (<5 years, 5-10 years, >10 years), and
20 whether they had been already using PEdDose in their daily work (yes, partly, no).
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25 26 **Sample size**

27 The sample size estimation was done in collaboration with the Clinical Trial Unit of the University of
28 Basel, Switzerland. An *a priori* error rate of 20% for the control study arm was assumed based on the
29 results of previous research estimating a 26.5% error rate for dose calculation using a pocket
30 calculator.[19] A 50% overall error reduction at a significance level of 5% with >80% power resulted in
31 a total of 600 items that need to be rated. We aimed to test the two arms for the confirmatory analysis
32 with six items per arm, which resulted in an estimated sample size of 50 participants (600 items / 12
33 items per participant = 50 participants) (Supplement 3). Adding an equal number of items for the
34 exploratory arm, the resulting total number of items that need to be rated was 900, which corresponds
35 to 18 items per participant.
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43 44 **Randomization**

45 Randomization was done on the level of the interventions and the items (Figure 1). Thus, for each
46 participant the order of the three interventions was randomized, while for each intervention six out of
47 the pool of 18 items were randomly drawn without replacement. The Gorilla Experimental Builder
48 enabled to design the randomization procedure directly into the trial, thus taking care of the
49 participant allocation.[18]
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54 55 **Statistical methods**

56 Statistical analyses were performed in R version 4.1.1.[20] The relevant functions and additional
57 packages used are denoted as *function* {package}. The only continuous variable was the secondary
58 outcome response time per item, which was transformed using the natural logarithm to achieve
59 normality of the residuals. Orthogonal sum-to-zero contrasts for the unordered factors 'institution'
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3 and 'profession' applying *contr.sum* {stats} were used. The lower-level effects were thus estimated at
4 the level of the grand mean and interpreted accordingly. We applied difference coding for the ordered
5 factors 'experience', 'PEDeDose user', and the exploratory version of the variable 'intervention' using
6 *contr.sdif* {MASS}.[21] Thus, each level of the ordered factors was compared to their previous level.
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8 The contrast coding scheme is provided in the supplement (Supplement 4).
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12 For the primary outcome 'error', we fitted a generalized linear mixed-effects model (GLMM) with a
13 logit-link function using *glmer* {lme4}.[22] The secondary outcome 'time' was assessed by fitting a
14 linear mixed-effects model (LMM) using *lmer* {lmerTest}.[23] All models were derived by starting with
15 maximal model specification based on the trial design, and then sequentially reducing model
16 complexity until a non-singular fit was achieved.[24] We started by defining by-subject and by-item
17 random intercepts and slopes (i.e. crossed-random effects) on each type of intervention. The main
18 variable 'intervention' and the additional covariates were treated as fixed variables.
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24 In exploratory analyses, we assessed the impact of structuring the dosing information by adding the
25 intervention *basic* (i.e. PEDeDose without the built-in calculator). Thus, the binary variable for the
26 intervention became an ordered three-level factor (*control, basic, full*). As a sensitivity analysis we
27 created a model that is only adjusted for the order of the interventions.
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32 For all models also an unadjusted model was built, containing only the variable 'intervention' as well
33 as only random intercepts for both subject and item, respectively. We derived Wald confidence
34 intervals. The *p*-values for the linear models were derived via Satterthwaite's degrees of freedom
35 method.[23] The estimated marginal means for the 'intervention' variable for all the models were
36 calculated using *emmeans* {emmeans}.[25] The summary outputs of the models are reported in the
37 supplement (Supplement 4).
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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 randomization order are visualized in Figure 2.

The characteristics of the participants are summarized in Table 1.

Table 1: Participant characteristics

Variable names	Number (%)
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)

Missing values and outliers

Of the total 936 items rated, there were four responses (0.4%) classified as missing, three in the *full* intervention, which were accidentally skipped and one 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 analyzed, 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 analyzed

Overall, 932 items were analyzed 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 analyzed, 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 (5%) errors for the *control*, *basic*, and *full* intervention, respectively. The median time [Q₁, Q₃] 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 generalized linear mixed-effects model with a logit-link was defined to estimate the adjusted odds ratio for dose derivation errors. The regression formula for the generalized linear mixed-effects model is shown below in R notation (I). The model included the covariates for institution and previous PDeDose 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) $error \sim intervention + institution + user (intervention | subject) + (intervention | item)$

(II) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 2: Effect of the intervention on error and time. The table shows the results of the confirmatory analyses comparing the CDSS PDeDose (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.

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			

Intervention full vs control	0.08	0.02 to 0.36	<.001
Institution Children's hospital	1.27	0.75 to 2.15	.382
Institution General hospital	1.12	0.74 to 1.70	.587
PEDeDose user partly vs no	0.57	0.27 to 1.29	.178
PEDeDose user yes vs partly	0.88	0.37 to 2.11	.771
Unadjusted model			
Intervention full vs control	0.15	0.08 to 0.27	<.001
Time			
	Time change (%)	95% Confidence interval	<i>p</i> -value
Multivariable model			
Intervention full vs control	-45	-51 to -39	<.001
Institution Children's hospital	-18	-26 to -8	<.001
Institution General hospital	3	-6 to 12	.585
Experience 5-10 y vs <5 y	3	-11 to 18	.722
Experience >10 y vs 5-10 y	1	-16 to 15	.862
PEDeDose user partly vs no	6	-9 to 26	.472
PEDeDose user yes vs partly	-8	-22 to 9	.357
Unadjusted model			
Intervention Full vs control	-45	-48 to -42	<.001

Ancillary analyses

Exploratory analyses

Additionally, we explored the impact of using structured dosing information while using a pocket calculator. The model formula of the generalized 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 to 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 (Supplement 4).

(III) $error \sim intervention + institution + user + (1 | subject) + (1 | item)$

(IV) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 3: Effect of the interventions on error and time. 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**.”

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			
Intervention basic vs control	0.67	0.44 to 1.03	.068
Intervention full vs basic	0.22	0.12 to 0.42	<.001
Institution Children's hospital	1.37	0.9 to 2.08	.143
Institution General hospital	0.97	0.68 to 1.38	.860
Experience 5-10 y vs <5 y	1.36	0.79 to 2.36	.273
Experience >10 y vs 5-10 y	1.15	0.64 to 2.05	.644

PEDeDose user partly vs no	0.51	0.26 to 1.00	.050
PEDeDose user yes vs partly	1.33	0.68 to 2.62	.402
Unadjusted model			
Intervention basic vs control	0.67	0.44 to 1.02	.063
Intervention Full vs basic	0.22	0.12 to 0.41	<.001
Time			
	Time change (%)	95% Confidence interval	<i>p</i> -value
Multivariable model			
Intervention basic vs control	-20	-27 to -12	<.001
Intervention full vs basic	-31	-38 to -23	<.001
Institution Children's hospital	-18	-26 to -10	<.001
Institution General hospital	3	-6 to 12	.545
Experience 5-10 y vs < 5 y	2	-11 to 17	.793
Experience >10 y vs 5-10 y	-2	-16 to 13	.749
PEDeDose user partly vs no	-1	-15 to 16	.913
PEDeDose user yes vs partly	-6	-20 to 10	.467
Unadjusted model			
Intervention basic vs control	-20	-24 to -16	<.001
Intervention full vs basic	-31	-35 to -27	<.001

Analysis of error types

For each error that occurred, we assumed the most plausible error type. The logging data of the PDeDose 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.

Table 4: Assumed error types identified based on the participants' response. Column values exceed the total error count when multiple error types were identified. The categories correspond to the CDSS PDeDose (*full*), PDeDose dosing information with a pocket calculator (*basic*), and the SmPC with a pocket calculator (*control*)

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 vs 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

N/A = error type not possible or not identifiable for this intervention.

*e.g. dosage was not converted to the dispensing unit

**e.g. the loading dose was used instead of the maintenance dose

Discussion

In this simulation trial, we showed that the CDSS PEdDose (*full*) significantly reduced the number of dose calculation errors and was more efficient when compared to either the structured PEdDose 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. Randomization 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 (e.g. 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 (e.g. dose adjustments due to renal insufficiency, comorbidities, or drug-drug interactions). However in this study, the impact of the CDSS PEdDose 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 pediatric label could be created. In pediatric 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.

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 PEdDose significantly improved the error rate as compared to the SmPC by reducing the odds of an error by a factor of 12. Furthermore, the CDSS PEdDose 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 (i.e. fixed effects) had a negligible impact on both outcomes. In contrast, there was high variability between participants and items, (i.e. random effects) leading to broad confidence intervals, especially in the two blocks using pocket calculator. However, the variability was drastically reduced when the CDSS PEdDose is used. This demonstrates that the CDSS PEdDose was able to mitigate the uncertainty produced by the human factor, while other factors such as experience do not suffice. Thus, the CDSS PEdDose increased the overall safety of the individually calculated dosages in our simulation. Furthermore, since there were no noteworthy differences between frequent PEdDose users, infrequent users, and new users, we could demonstrate that the usability of the CDSS PEdDose 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 PEdDose with pocket calculator and the CDSS PEdDose was still striking with five-fold 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 PEdDose as the built-in calculator does respect the maximum dose. This again highlights the importance of providing HCPs with individualized 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 PEdDose logging data revealed that most of the errors committed with the CDSS PEdDose could be prevented with a reasonable integration into the prescribing software, such as wrong birthdate entries or transcription errors.

Generalizability

Based on the strong results and the inevitability of human errors, we are confident that the use of the CDSS PEdDose will generally enhance the safety of prescribed dosages in practice. Furthermore, the time reduction that is achieved with the use of the CDSS PEdDose 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 PEdDose. This is in contrast to real-world studies where the magnitude of the measured effect

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3 will be modified by the way the CDSS is integrated into a primary software (i.e. a clinical information
4 system), CDSS uptake (i.e. percentage of CDSS use),[27] vigilant HCPs,[11,28] or by other measures
5 implemented to prevent such types of errors. These factors might influence the effect in different
6 ways. A bad integration of the CDSS in a clinical information system will compromise usability, uptake,
7 and can enable additional types of errors to occur. On the other hand, a good integration will simply
8 rule out even more types of errors by design (e.g. transcription errors). Interestingly, clinical
9 information system providers do not need to conduct usability tests as compared to European medical
10 device manufacturers.[29,30] Last but not least, we think that it is undisputable that we should prevent
11 the occurrence of an error in the first place by using a dose calculator rather than to rely on post-hoc
12 measures or on the commendable vigilance of the HCPs.[10,11,28]

20 **Comparison with literature**

21
22 Even though there are a multitude of dosing calculators freely available, surprisingly, almost all lack a
23 *conformité européenne* (CE) marking.[31] Furthermore, there are only few contemporary studies that
24 assess dose prescribing errors in a simulation.[19,32,33] Siebert and colleagues found significant error
25 reduction with the use of a mobile app during drug preparation in pediatric emergency
26 settings.[32,33]. Interestingly, the baseline error rates in both studies were strikingly high with values
27 of 63% [33] and 75% [32] as compared to the 23% in our study. However, comparison is limited as they
28 did not assess the dose calculation step in isolation. Thus, we want to highlight the most similar study
29 by van der Zanden *et al.* that assessed the former website-integrated dosing calculator of the Dutch
30 Pediatric Formulary.[19,34] However, the calculator is not available anymore. They found 26% and
31 17% clinically relevant errors in the manual group and in the calculator group, respectively. This
32 resulted in a non-significant estimated mean difference of 7% in favor of the calculator group.
33 However, they used a between-subject design and a two-minute time limit per item. We think that the
34 use of a within-subject instead of a between-subject design was a major strength in our study.
35 Furthermore, we did not impose a time limit, as otherwise we could not estimate the time needed for
36 the dose derivation. A time limit probably would have increased the manual error rate even further,
37 but the results would be influenced by the participants' reading speed.

50 **Conclusion and outlook**

51
52 We demonstrated that the CDSS PEdDose with its built-in calculator significantly reduced the error
53 rate and time needed for the dose derivation for pediatric patients and neonates when compared to
54 the SmPC in a simulation trial. The high variability in error rates within HCPs could be mitigated when
55 PEdDose was used. Interestingly, no substantial improvement of structured (*basic*) versus full-text
56 (*control*) dosing information was found. Our simulation showed that by limiting the human factor and
57 by providing guidance during the dose derivation step, dose calculation errors can be reduced. A
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3 reasonable integration of the CDSS into the electronic workflow of pediatric prescribing may even
4 further limit the human factor during the prescribing step, and thus could prevent additional error
5 types by design.
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Confidential: For Review Only

Other information

Data availability

The data and the R scripts for the statistical analysis are provided in the supplements 5, 6, and 7.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Conflicts of interest

LH as a PhD student is funded by PEDeus Ltd. LH, KK, MW and PV are employees of PEDeus Ltd. MG is a member of the board of directors of PEDeus Ltd as well as the medical director of the University Children's Hospital Zurich. None of the authors has any ownership in either institution. The PEDeus Ltd. is a 100% subsidiary company of the University Children's Hospital Zurich. The authors have no additional conflicts of interest to declare that are relevant to the content of this article.

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Figures

Figure 1: Visualization of the trial design. The name of the interventions correspond to the CDSS PEdDose with built-in calculator (full), PEdDose used together with a pocket calculator (basic), and Summary of Product Characteristics used together with a pocket calculator (control)

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 PEdDose with built-in calculator (full), PEdDose used together with a pocket calculator (basic), and Summary of Product Characteristics with pocket calculator (control).

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

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 PEdDose with built-in calculator (full), PEdDose used together with a pocket calculator (basic), and Summary of Product Characteristics with pocket calculator (control).

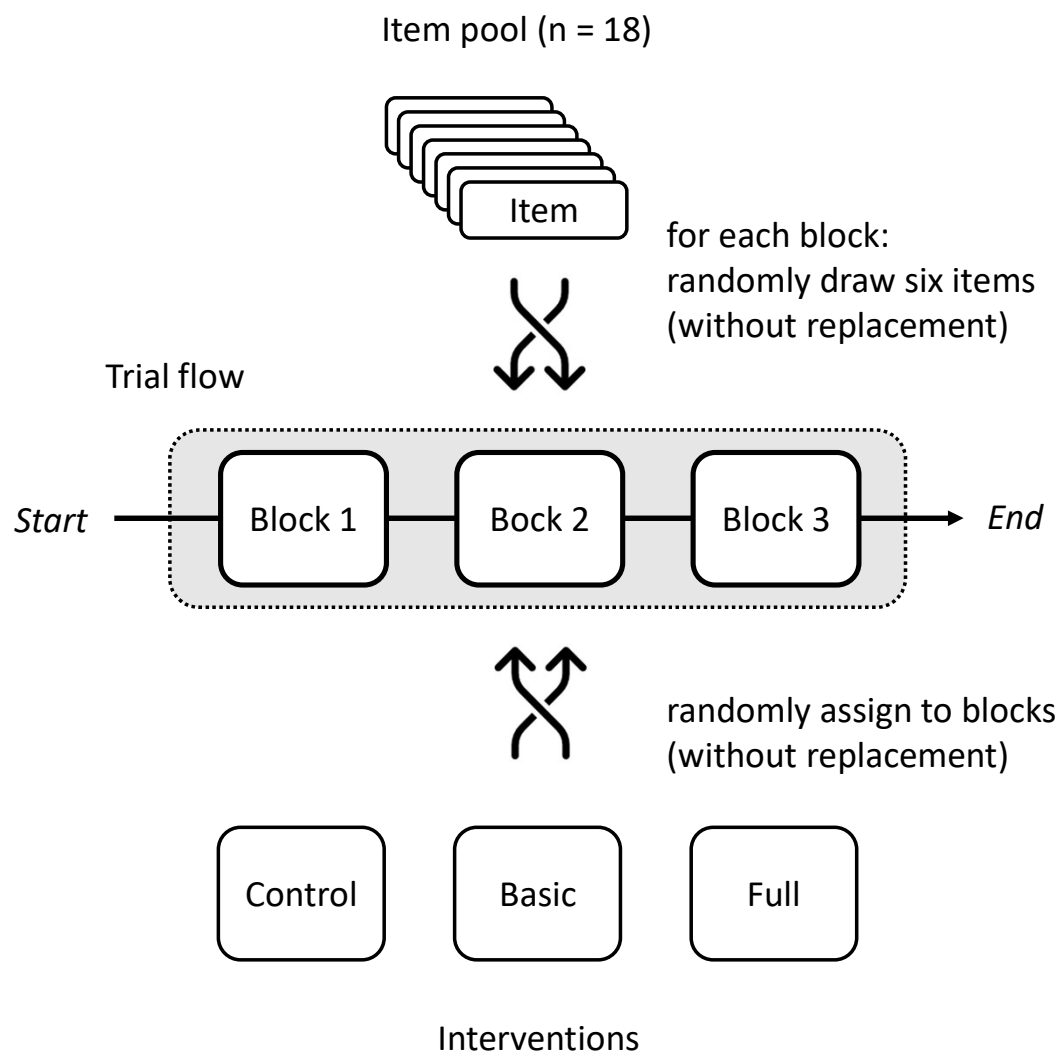
Figure 5: Number of errors stratified by intervention order and type. The name of the interventions correspond to the CDSS PEdDose with built-in calculator (full), PEdDose used together with a pocket calculator (basic), and Summary of Product Characteristics with pocket calculator (control).

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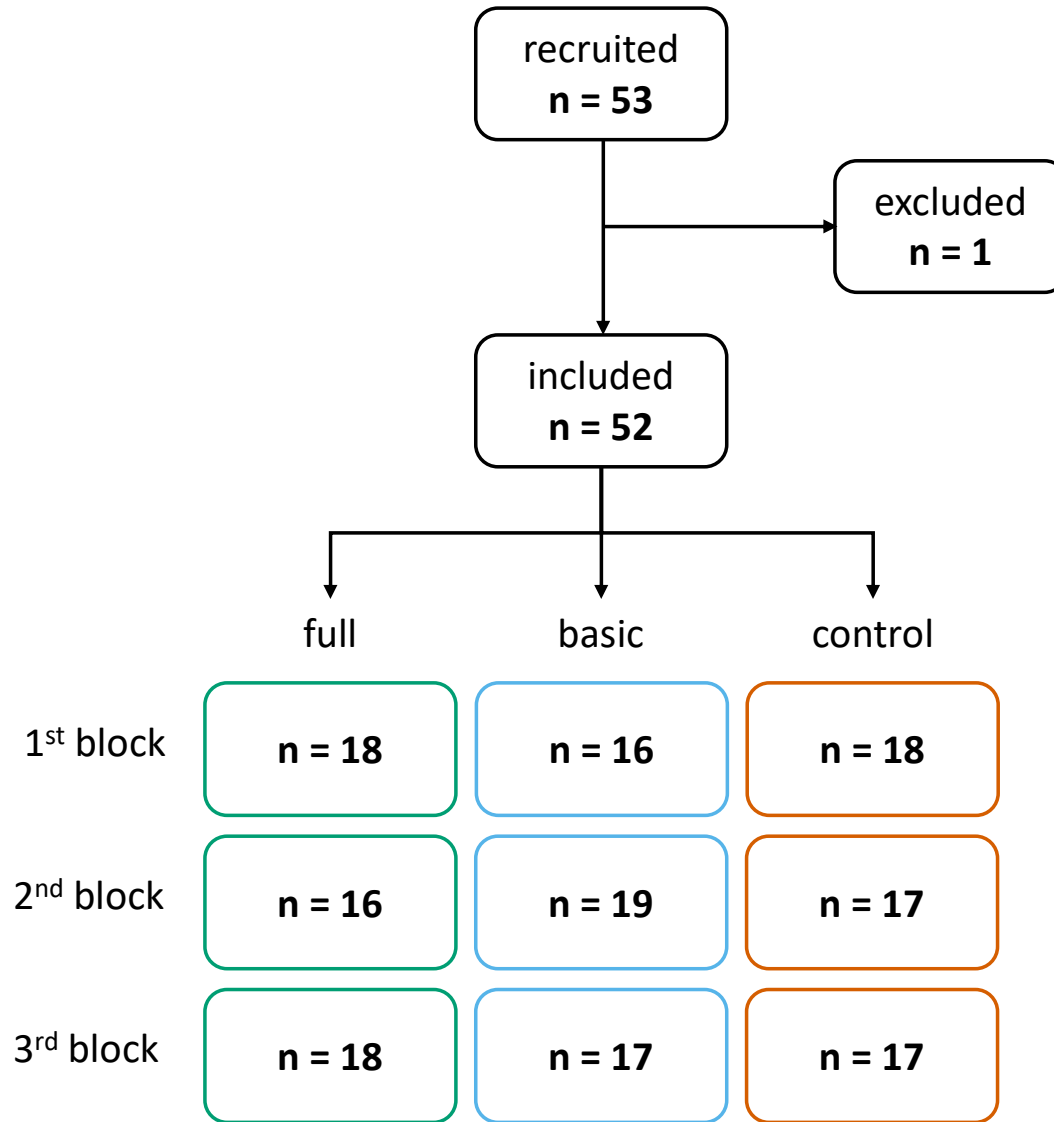
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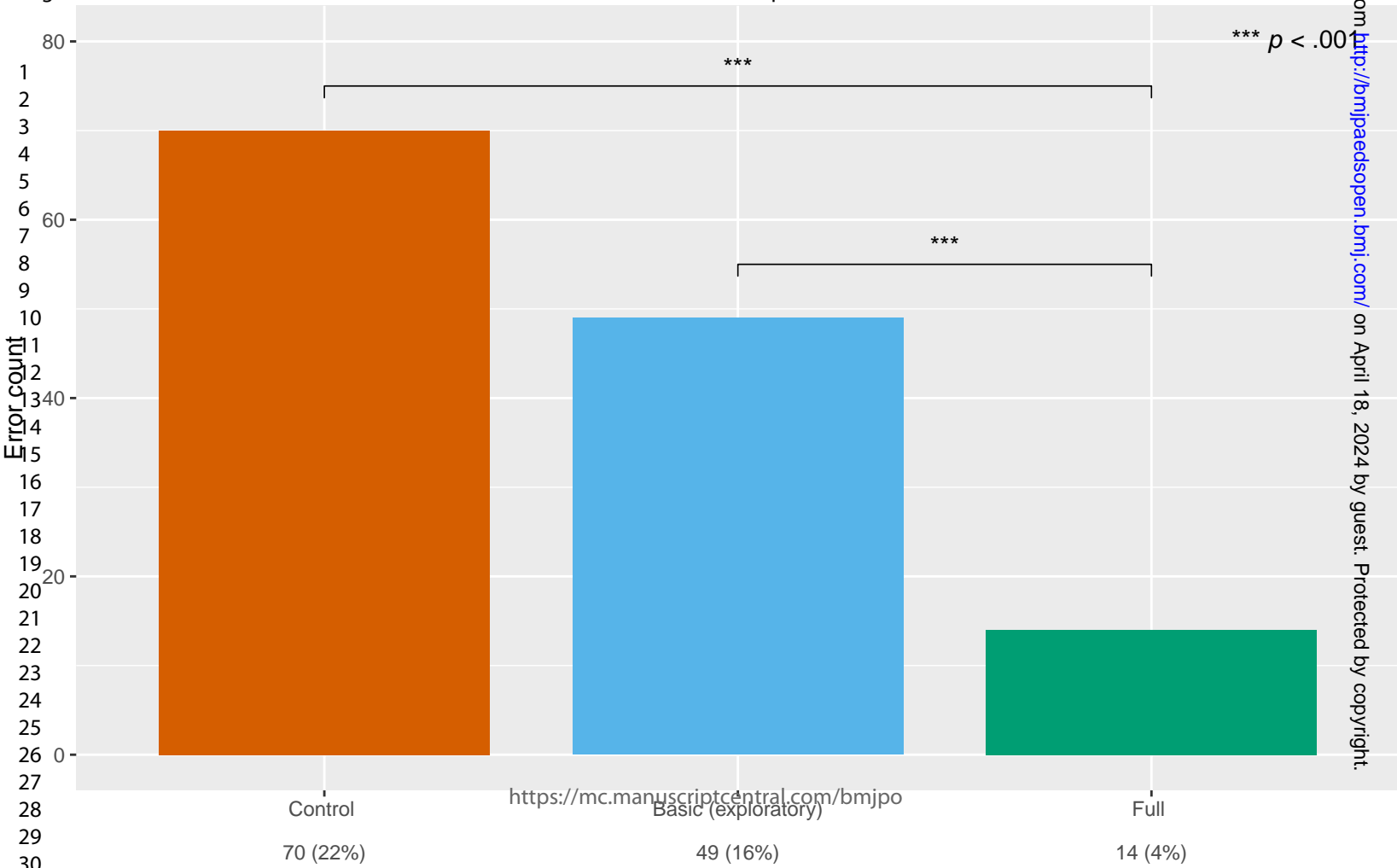


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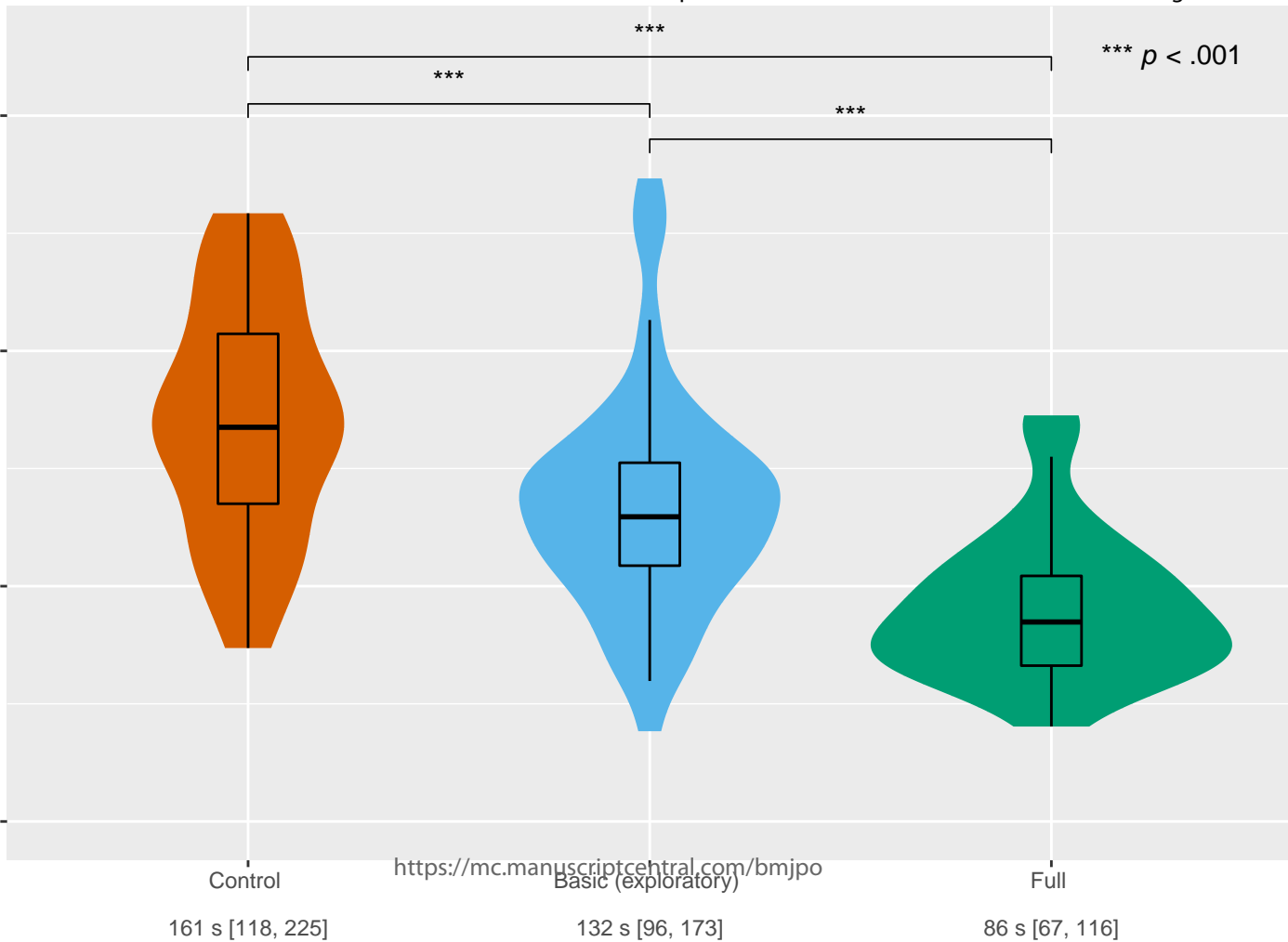
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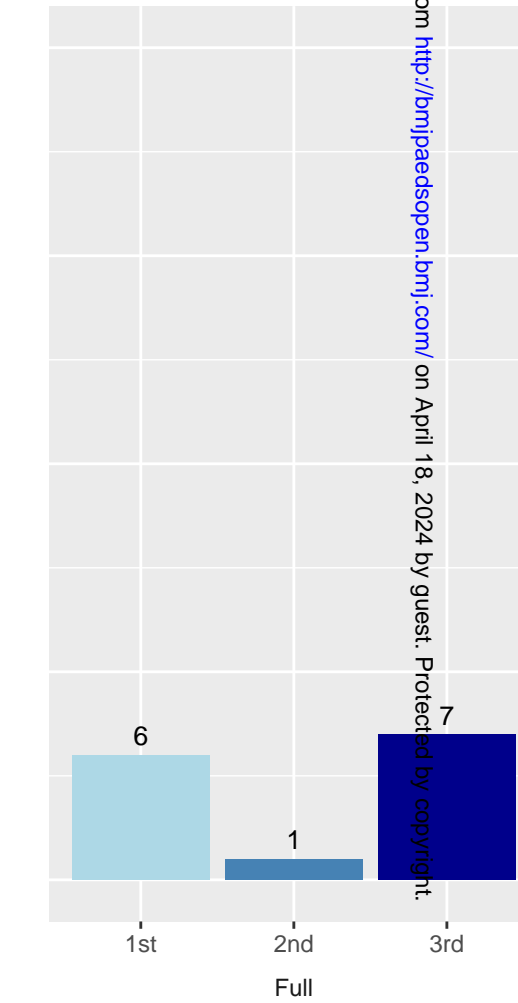
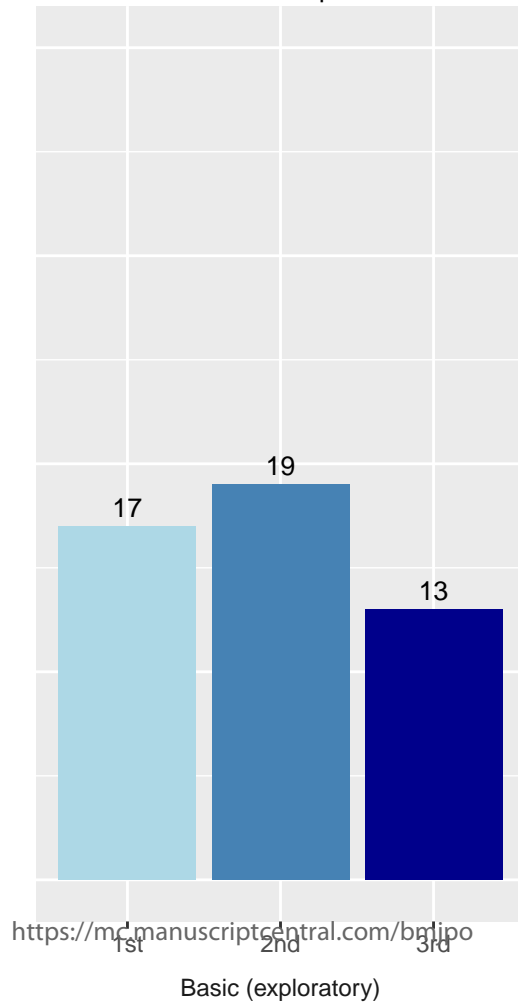
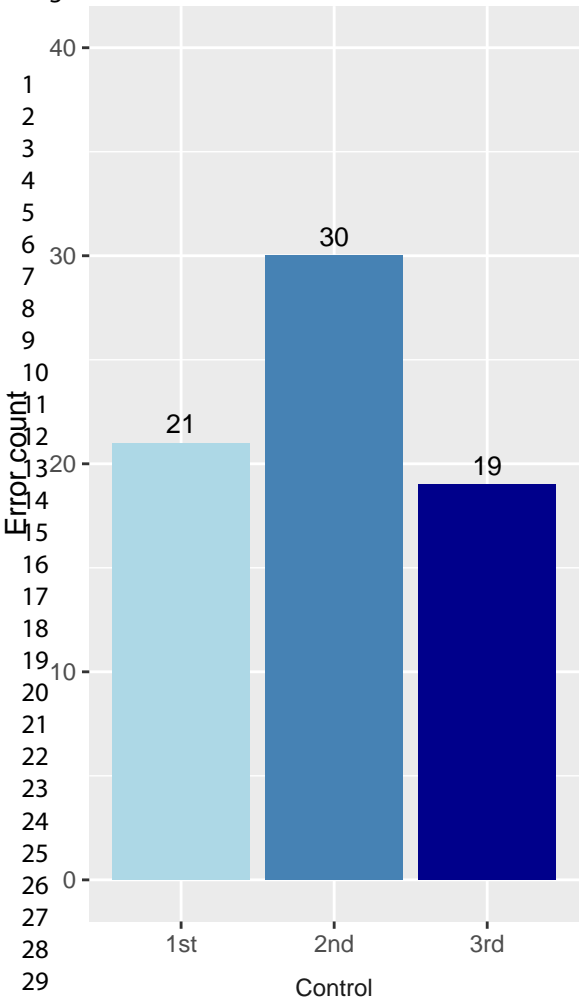
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Supplement 1 – Description of items

ID	Dosing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
1	mL/dose	infection in cystic fibrosis patients	Ciprofloxacin	p.o. (liquid)	-	2x daily	6y 10mth	26	-	no
2	mg/dose	bacterial infection (severe)	Vancomycin	i.v.	-	4x daily	5wks ^d	4.18	-	yes – GA 35 2/7
3	drops/dose	epilepsy	Clonazepam ^b	p.o. (liquid)	loading dose / begin	3x daily	6y 7mth	29	-	no
4	mL/dose	acute otitis media	Amoxicillin – Clavulanic acid	p.o. (liquid)	-	2x daily	2y 8mth	14	-	no
5	mL/dose	candidiasis (systemic)	Fluconazole	p.o. (liquid)	-	1x daily	8y	31	-	no
6	mg/dose	bacterial infection (severe)	Flucloxacillin	i.v.	-	3x daily	6d	3.2	-	no

ID	Dispensing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
7	mg/dose	nausea and vomiting in chemotherapy	Dexamethasone dihydrogen phosphate disodium	i.v.	-	4x daily	1y 6mth	12	81	no
8	mg/dose	arthritis	Methotrexate ^b	s.c.	-	1x weekly	12y 5mth	36	138	no
9	mL/dose	prophylaxis of acute rejection in patients with allogenic kidney transplantation (in combination with ciclosporin and corticosteroids)	Mycophenolate mofetil ^b	p.o. (liquid)	-	2x daily	9y 3mth	32	122	no
10	mg/dose	fungal infection (invasive)	Caspofungin	i.v.	loading dose / begin	-	11mth	9.5	76	no
11	mL/dose	bacterial infection	Clarithromycin	p.o. (liquid)	-	2x daily	7mth	7.6	-	no
12	mg/dose	tuberculosis	Isoniazid	p.o.	-	1x daily	10y 7mth	38	-	no

ID	Dispensing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
13	mL/dose	nausea and vomiting in chemotherapy	Ondansetron	p.o. (liquid)	follow-up treatment	3x daily	14y 10mth	46	BSA ^c : >1.2 m ²	no
14	mg/dose	bacterial infection	Ceftriaxone	i.m.	-	1x daily	5wks ^d	3.82	-	yes – GA 36 5/7
15	mL/dose	pruritus	Hydroxyzine dihydrochloride	p.o. (liquid)	-	3x daily	5y 4mth	24	-	no
16	mg/dose	intoxication with benzodiazepines	Flumazenil	i.v.	loading dose / begin	-	8y 6mth	36	-	no
17	mL/dose	insomnia	Chloral hydrate	p.o. (liquid)	-	1x daily	5y 1mth	22	-	no
18	mg/dose	urolithiasis (urates / urinary stones)	Allopurinol	p.o.	-	1x daily	13y 1mth	42	-	no

^a Age was shown to participants as birthdate calculated on the day of the experiment

^b Substance with narrow therapeutic window

^c BSA = body surface area (for this item the BSA was provided for the SmPC user as the dosing information differentiated between BSA >1.2 m² or <1.2 m²)

^d corrected age

Supplement 2 – Example of the structured dosing information of PEDeDose

Substance		Vancomycin									
Indication		bacterial infection, severe									
Route of administration		IV, parenteral									
Calculated dose											
Age	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
5 wk	4.18 kg		IV		63 mg/dose	4 x daily			by inf	B	
Date of birth 03.08.2022		Weight 4.18 kg	PI Yes	GA 35 2/7 WOP	corrA 5 wk	PNA 10 wk					
You must enter the height to be able to calculate the BMI.											
Products in Switzerland matching the data set of the calculated dose											
General doses											
Age/PMA	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
< 30 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 24 h after the loading dose; by inf	D	
< 30 wk		PI	IV	maintenance	20 mg/kg/dose	1 x daily			first maintenance dose 24 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 18 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	maintenance	20 mg/kg/dose	every 18 h			first maintenance dose 18 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 12 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	maintenance	20 mg/kg/dose	2 x daily			first maintenance dose 12 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	(A)	
28 D - 18 Y and < 66 kg			IV		15 mg/kg/dose	4 x daily			by inf	B	
< 18 Y and ≥ 66 kg			IV		1000 mg/dose	4 x daily			by inf	B	

Figure: Example of the vancomycin dosage information for severe bacterial infection to be administered intravenously. In the calculated dosage tab one can see the calculated dosage for a hypothetical preterm of 5 weeks of age (corrected age) with a weight of 4.18 kg analogous to item number 2 of the trial. In the general doses tab the basic dosing information can be seen.

Supplement 3 – Sample size estimation

Expected power for significant improvement of the CDSS PEDeDose vs no CDSS

Error rate without CDSS: 20%

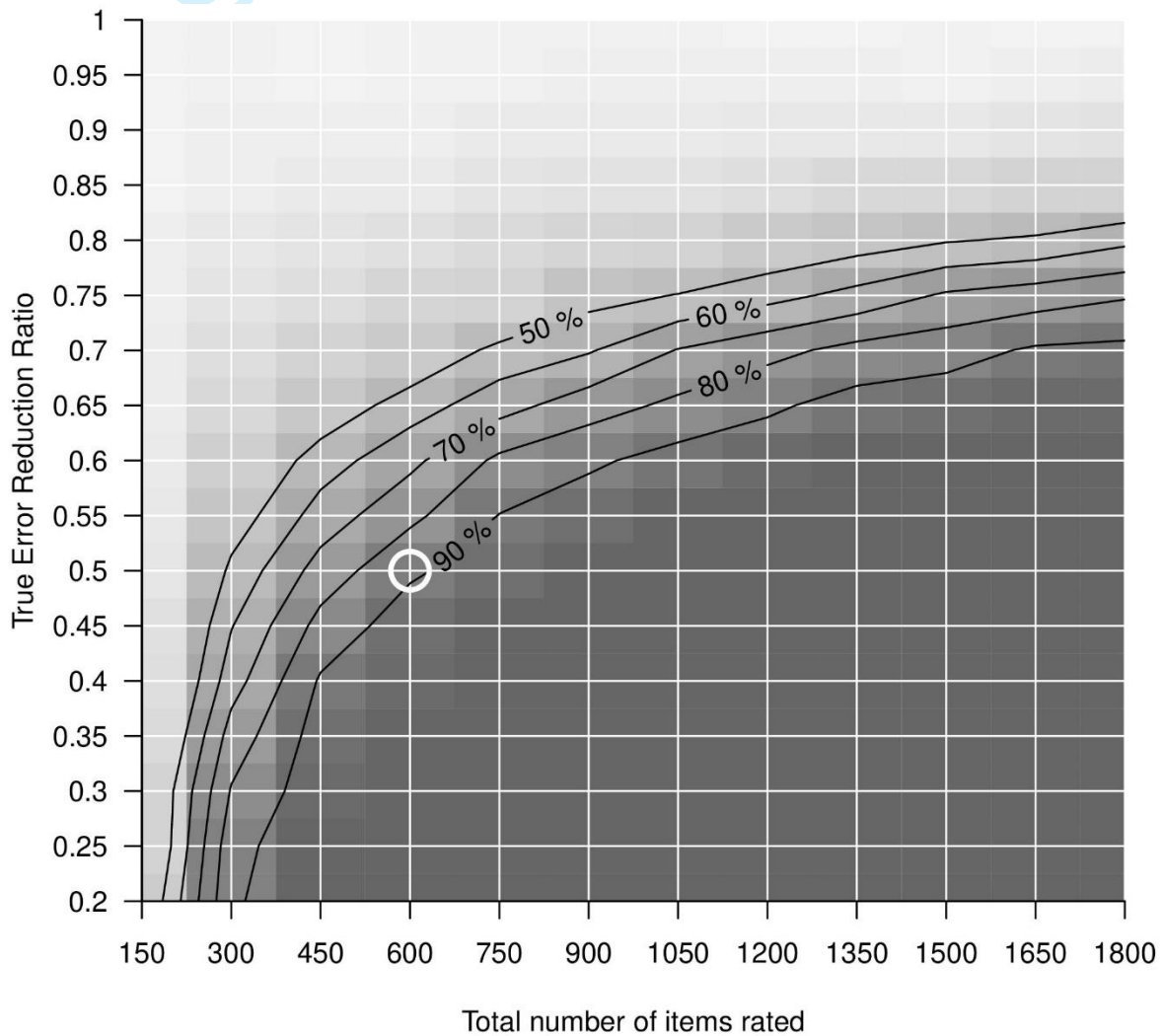


Figure: The experiment was simulated 999 times assuming between 150 to 1800 items that are rated, while achieving an error reduction ratio between 0.2 to 1 (no reduction). The white circle marks the estimated number of items that need to be rated to achieve a 50% error reduction.

Supplement 4 - Statistical analyses

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Confirmatory analysis

Errors (full model)

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention	0.08	0.02	0.36	<0.001
Institution (Children's hospital)	1.27	0.75	2.15	0.3823
Institution (Hospital)	1.12	0.74	1.70	0.5875
User (partly vs no)	0.57	0.26	1.29	0.1779
User (yes vs partly)	0.88	0.37	2.11	0.7712

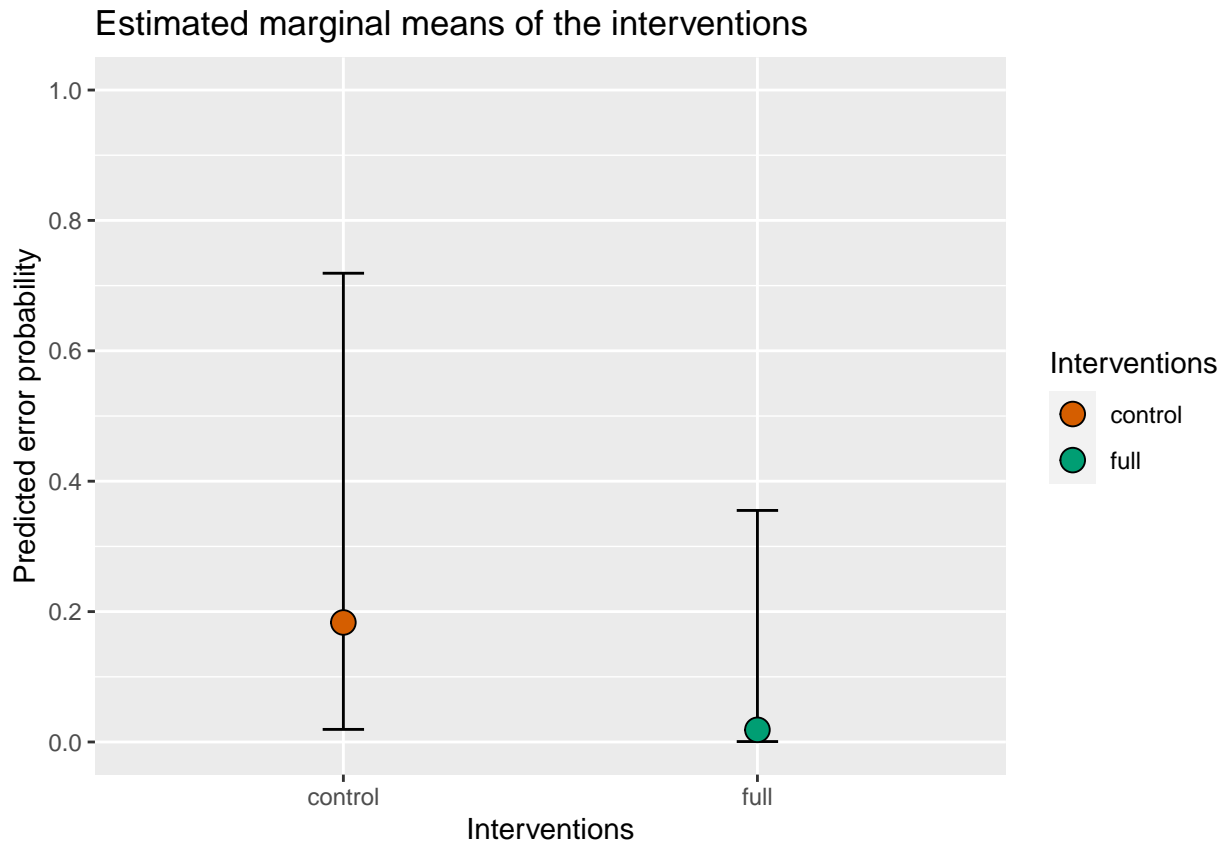
R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula:
## error ~ intervention + institution + user + (intervention | subject) +
## (intervention | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC    logLik deviance df.resid
##  457.2   510.4   -216.6   433.2     608
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8811 -0.4334 -0.2101 -0.1185  3.7005
##
## Random effects:
##  Groups Name          Variance Std.Dev. Corr
##  subject (Intercept)    0.2340  0.4838
##           interventionfull 1.4835  1.2180 -0.51
##  item   (Intercept)    0.2954  0.5435
##           interventionfull 0.7559  0.8694 -0.35
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -1.4938    0.2415  -6.187 6.15e-10 ***
## interventionfull -2.4694    0.7395  -3.339 0.000839 ***
## institution1     0.2359    0.2700   0.874 0.382263
## institution2     0.1151    0.2121   0.543 0.587464
## userpartly-no   -0.5563    0.4129  -1.347 0.177867
## useryes-partly  -0.1302    0.4478  -0.291 0.771219
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
```



```
##          (Intr) intrvn instt1 instt2 usrpr-  
## intrvntnfl1 -0.252  
## institutin1 -0.139 -0.091  
## institutin2 -0.137  0.034 -0.404  
## userprtly-n  0.238  0.040 -0.297  0.165  
## usry-sprtly -0.129  0.144 -0.390  0.164 -0.467
```

Plot - Predicted probability of error



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Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention	0.15	0.08	0.27	<0.001

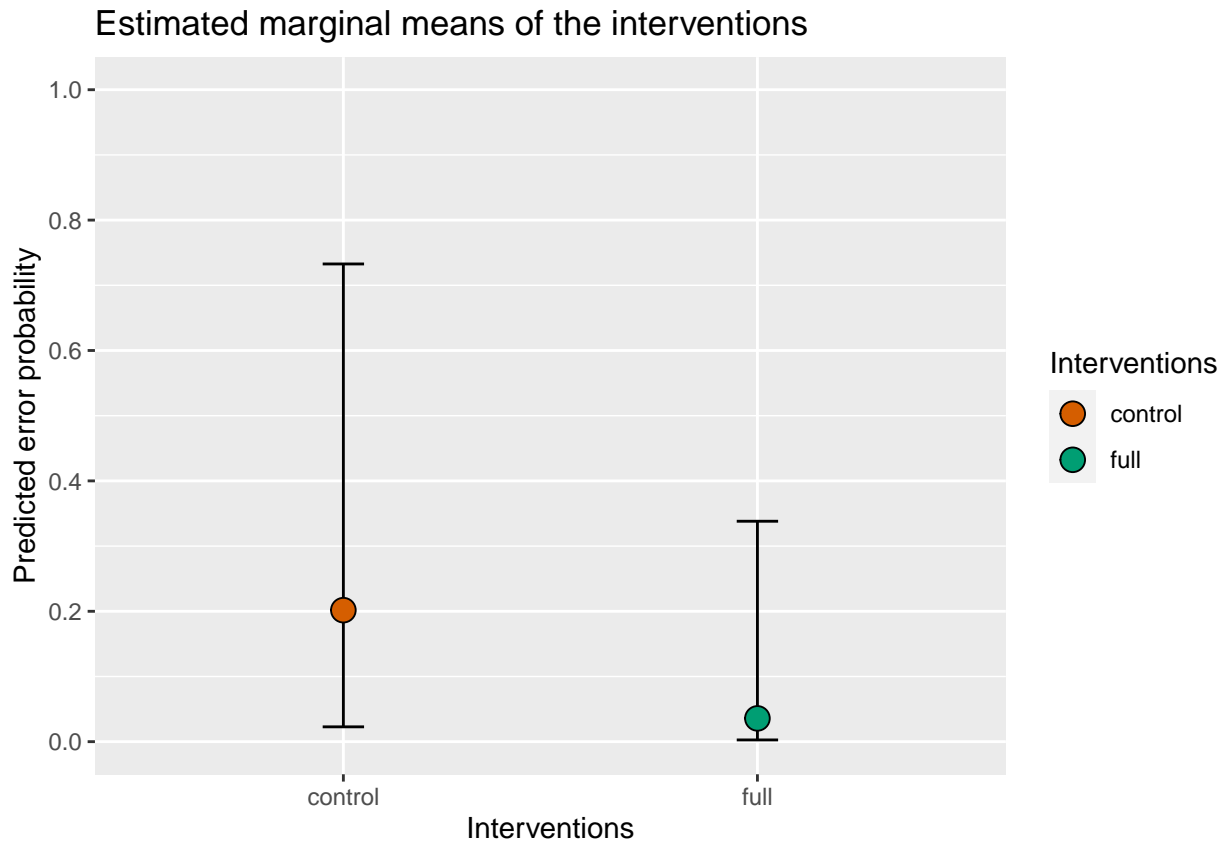
R summary output

```

## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##           AIC          BIC    logLik deviance df.resid
##      447.0      464.8   -219.5   439.0      616
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8104 -0.4473 -0.2367 -0.1683  5.8528
##
## Random effects:
##  Groups Name          Variance Std.Dev.
##  subject (Intercept) 0.2236   0.4728
##  item    (Intercept) 0.2925   0.5408
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -1.3756    0.2165  -6.355 2.09e-10 ***
## interventionfull -1.9200    0.3183  -6.032 1.62e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.242

```

Plot - Predicted probability of error



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Time (full model)

Results

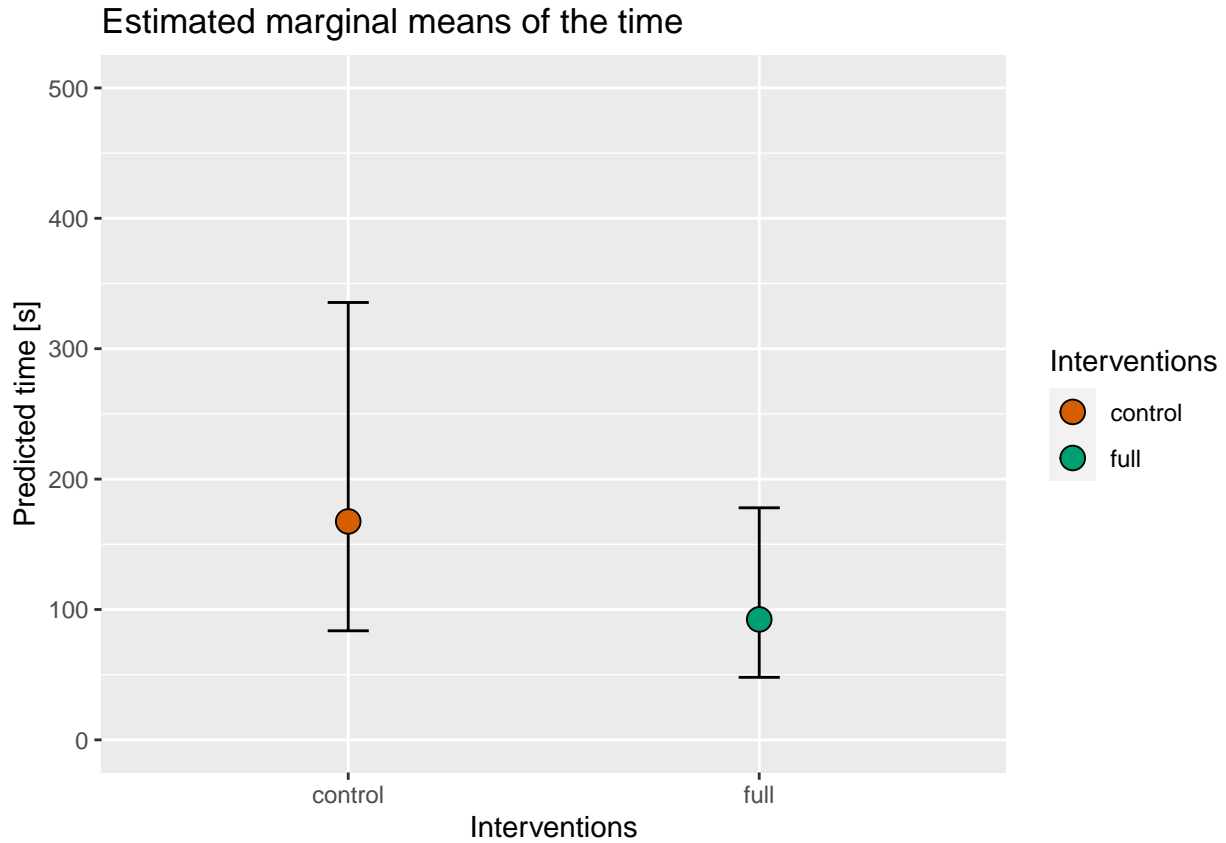
Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-44.85	-50.51	-38.54	<0.001
Institution (Children’s hospital)	-17.78	-26.16	-8.46	<0.001
Institution (Hospital)	2.60	-6.37	12.42	0.5853
Experience (5-10y vs <5y)	2.64	-10.99	18.36	0.7217
Experience (>10y vs 5-10y)	-1.39	-15.75	15.40	0.8619
User (partly vs no)	6.34	-9.92	25.52	0.4717
User (yes vs partly)	-7.73	-22.11	9.30	0.3568

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_confirmatory
##
## REML criterion at convergence: 432.7
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -3.4708 -0.6145 -0.0595  0.5344  3.1635
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject (Intercept)          0.04406  0.2099
##           interventionfull 0.05292  0.2300  -0.35
##   item     (Intercept)          0.06619  0.2573
##           interventionfull 0.02677  0.1636  -0.91
## Residual                0.08039  0.2835
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    5.12111    0.07072 26.21325  72.415 < 2e-16 ***
## interventionfull -0.59507    0.05524 30.37710 -10.773 6.74e-12 ***
## institution1    -0.19580    0.05480 44.96048  -3.573 0.000856 ***
## institution2     0.02564    0.04665 44.84160   0.550 0.585265
## experience5-10y-<5y  0.02606    0.07269 44.77178   0.359 0.721652
## experience>10y-5-10y -0.01404    0.08025 44.96372  -0.175 0.861888
## userpartly-no     0.06144    0.08463 44.84683   0.726 0.471654
## useryes-partly   -0.08049    0.08645 45.06018  -0.931 0.356777
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvn instt1 instt2 e5-10- e>10-5 usrpr-
```

```
## intrvntnfl1 -0.698
## institutin1 -0.071 -0.001
## institutin2 -0.064 0.000 -0.412
## expr5-10-<5 0.039 -0.002 -0.027 -0.311
## exp>10-5-10 0.062 0.000 0.159 0.035 -0.442
## userprtly-n 0.114 0.002 -0.292 0.199 -0.043 -0.047
## usrys-prtly -0.073 -0.001 -0.375 0.134 0.000 0.007 -0.466
```

Plot - Predicted response time



Only

Time (simple model)

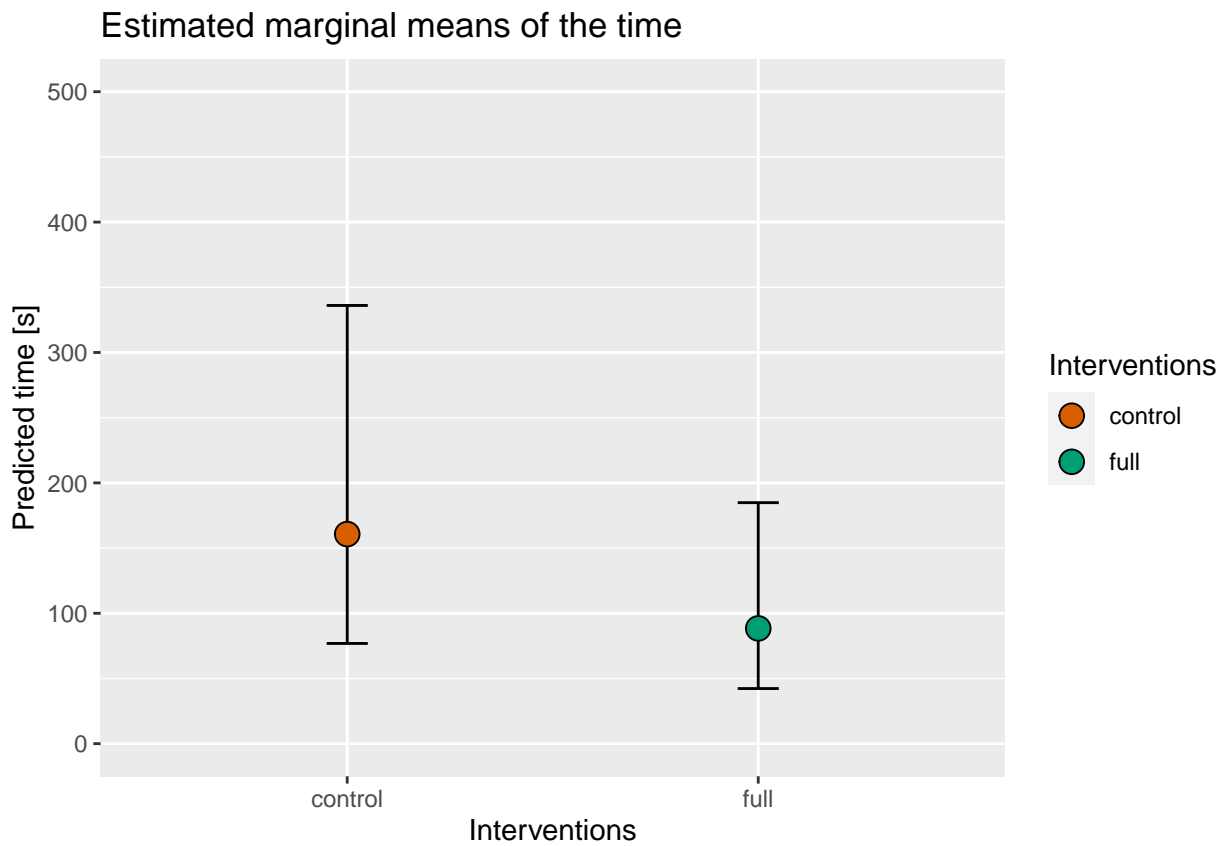
Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-45	-47.73	-42.12	<0.001

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
##
## REML criterion at convergence: 494.8
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -4.0767 -0.6149 -0.0248  0.5679  3.3763
##
## Random effects:
##   Groups   Name                Variance Std.Dev.
##   subject (Intercept)  0.05797  0.2408
##   item     (Intercept)  0.03607  0.1899
##   Residual                    0.10085  0.3176
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error      df t value Pr(>|t|)
## (Intercept)    5.07975    0.05877  38.59148   86.44 <2e-16 ***
## interventionfull -0.59777    0.02604  551.44043  -22.95 <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.222
```

Plot - Predicted response time



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Exploratory analysis

Errors (full model)

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0677
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Institution (Children's hospital)	1.37	0.90	2.08	0.1428
Institution (Hospital)	0.97	0.68	1.38	0.8601
Experience (5-10y vs <5y)	1.36	0.79	2.36	0.2725
Experience (>10y vs 5-10y)	1.15	0.64	2.05	0.6443
User (partly vs no)	0.51	0.26	1.00	0.0498
User (yes vs partly)	1.33	0.68	2.62	0.4019

R summary output

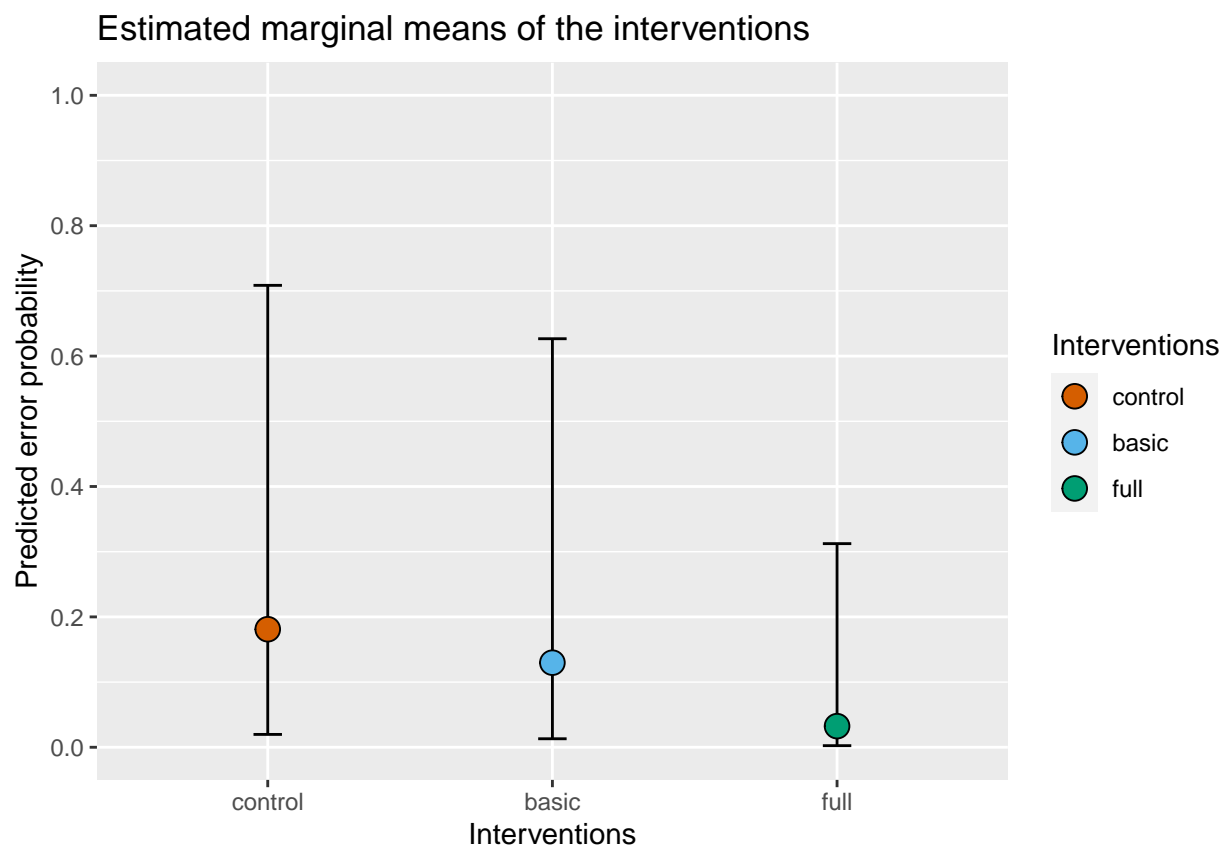
```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + institution + experience + user + (1 |
## subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##    711.6    764.9   -344.8   689.6     921
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0078 -0.4323 -0.2991 -0.1736  6.2086
##
## Random effects:
##  Groups Name          Variance Std.Dev.
##  subject (Intercept) 0.1555    0.3943
##  item    (Intercept) 0.3354    0.5791
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -2.26943   0.21046 -10.783 < 2e-16 ***
## interventionbasic-control -0.39394   0.21565  -1.827  0.0677 .
## interventionfull-basic   -1.49297   0.31775  -4.699 2.62e-06 ***
## institution1             0.31265   0.21334  1.466  0.1428
## institution2            -0.03148   0.17857  -0.176  0.8601
## experience5-10y-<5y      0.30767   0.28040  1.097  0.2725
## experience>10y-5-10y    0.13731   0.29742  0.462  0.6443
## userpartly-no           -0.67513   0.34415  -1.962  0.0498 *
## useryes-partly          0.28866   0.34439  0.838  0.4019
## ---
```

```

1
2
3  ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
4  ##
5  ## Correlation of Fixed Effects:
6  ##          (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
7  ## intrvntnbs-  0.043
8  ## intrvntnfl-  0.277 -0.374
9  ## institutin1 -0.173 -0.002   -0.010
10 ## institutin2 -0.098 -0.006   -0.005   -0.345
11 ## expr5-10-<5  0.019  0.000   -0.010   -0.042 -0.314
12 ## exp>10-5-10  0.061 -0.004    0.005    0.146  0.070 -0.431
13 ## userprtly-n  0.239  0.007    0.007   -0.312  0.178 -0.039 -0.037
14 ## usry-sprtly -0.137 -0.009    0.002   -0.324  0.113  0.023  0.025 -0.529
15
16

```

Plot - Predicted probability of error



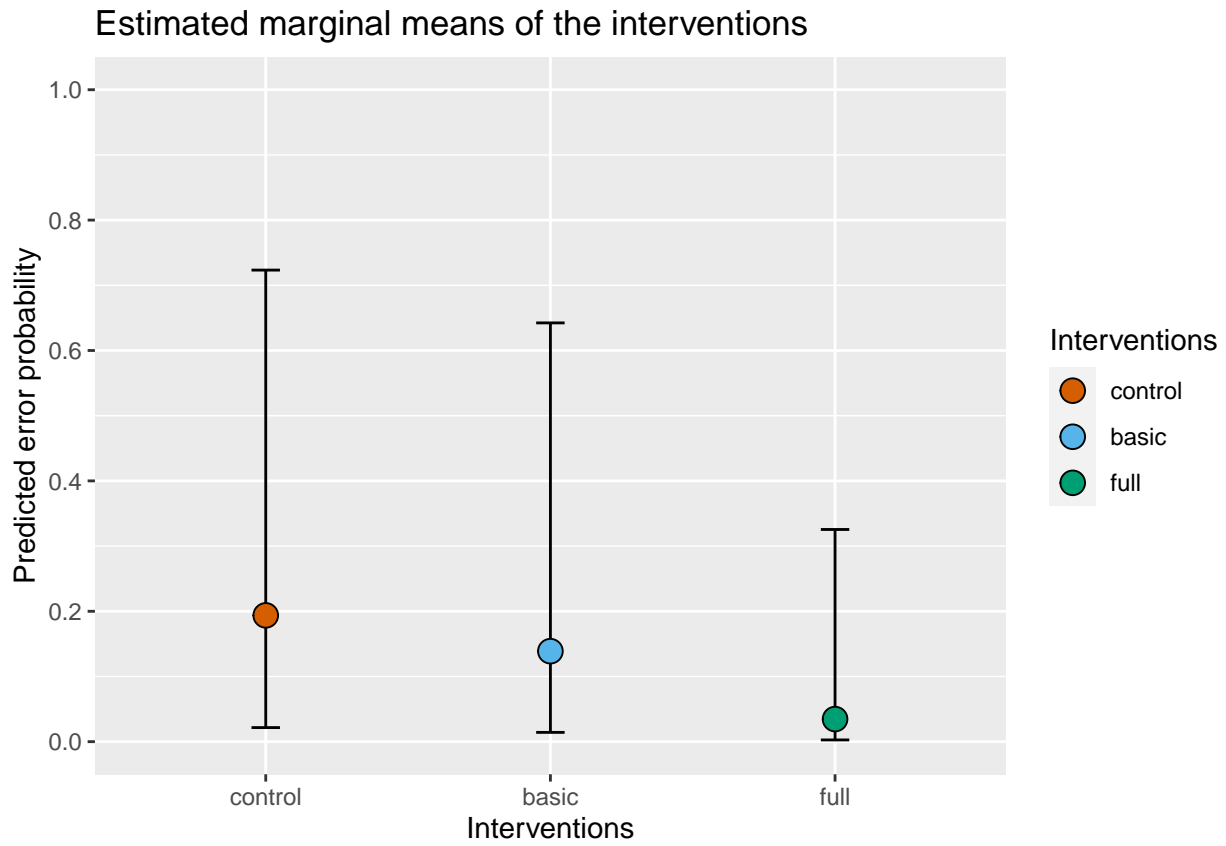
Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.02	0.0629
Intervention (full vs basic)	0.22	0.12	0.41	<0.001

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##    706.8    731.0   -348.4   696.8     927
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.9847 -0.4297 -0.3089 -0.1722  5.7553
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2545   0.5044
##  item    (Intercept) 0.3500   0.5916
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1927    0.2047 -10.710 < 2e-16 ***
## interventionbasic-control -0.3994    0.2148  -1.860  0.0629 .
## interventionfull-basic  -1.5014    0.3169  -4.738 2.16e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.044
## intrvntnfl-  0.282 -0.375
```

Plot - Predicted probability of error



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Time (full model)

Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.95	-27.14	-12.06	<0.001
Intervention (full vs basic)	-30.99	-38.42	-22.67	<0.001
Institution (Children's hospital)	-18.44	-26.38	-9.64	<0.001
Institution (Hospital)	2.75	-5.83	12.12	0.5453
Experience (5-10y vs <5y)	1.85	-11.10	16.69	0.7926
Experience (>10y vs 5-10y)	-2.43	-16.02	13.36	0.7493
User (partly vs no)	-0.88	-15.39	16.12	0.9133
User (yes vs partly)	-5.87	-19.92	10.63	0.4666

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_exploratory
##
## REML criterion at convergence: 653.6
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -4.1903 -0.5998 -0.0537  0.5331  3.2470
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject (Intercept)          0.03751  0.1937
##           interventionbasic-control 0.03513  0.1874  0.10
##           interventionfull-basic    0.06151  0.2480  0.02 -0.47
##   item     (Intercept)          0.04184  0.2045
##           interventionbasic-control 0.01928  0.1388  0.01
##           interventionfull-basic    0.02960  0.1721 -0.76 -0.48
## Residual                        0.08292  0.2880
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    4.842339   0.057639 30.008155  84.011 < 2e-16 ***
## interventionbasic-control -0.222575   0.048001 28.046824  -4.637 7.46e-05 ***
## interventionfull-basic   -0.370936   0.058103 30.941660  -6.384 4.17e-07 ***
## institution1    -0.203848   0.052280 44.997416  -3.899 0.000319 ***
## institution2     0.027128   0.044511 44.920751   0.609 0.545288
## experience5-10y-<5y    0.018346   0.069372 44.871124   0.264 0.792633
## experience>10y-5-10y -0.024608   0.076541 44.953549  -0.321 0.749324
## userpartly-no    -0.008842   0.080746 44.900724  -0.110 0.913292
## useryes-partly   -0.060522   0.082432 45.008740  -0.734 0.466626
## ---
```

Time (full model)

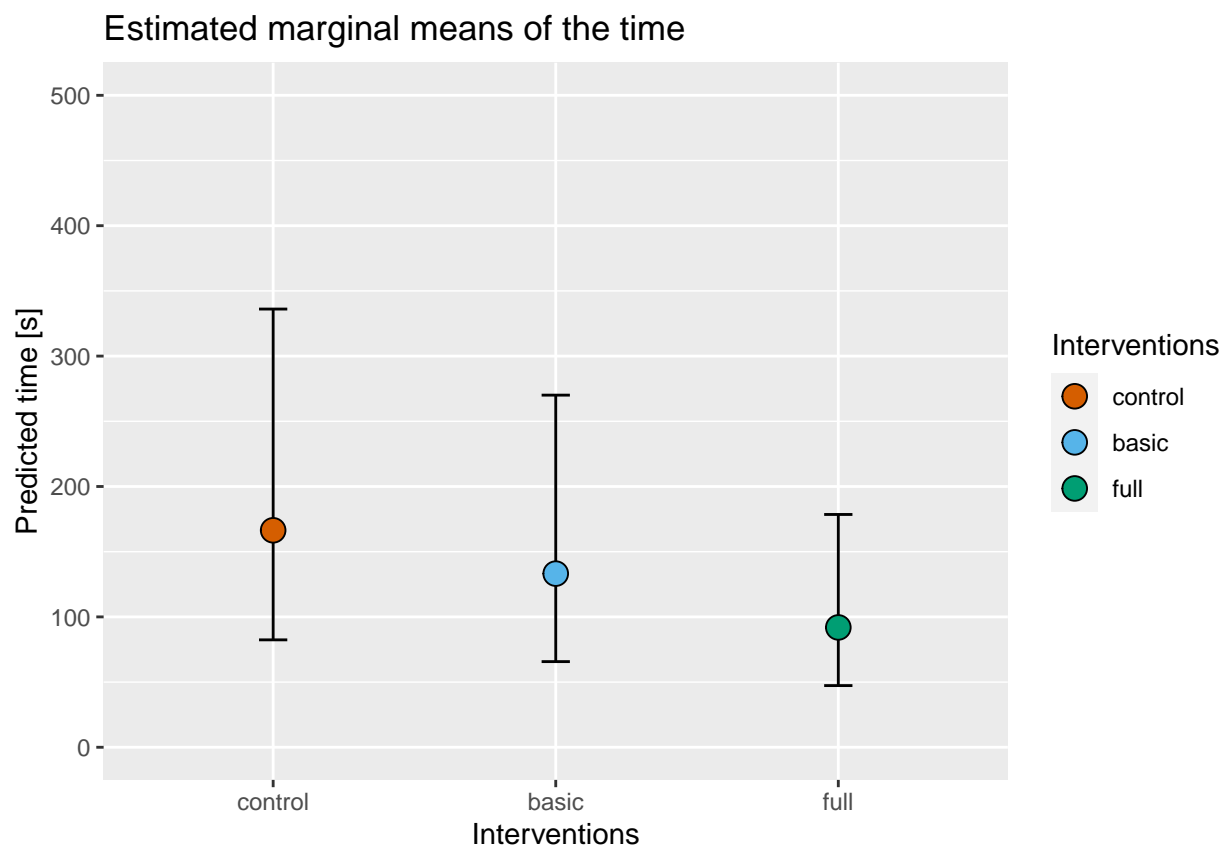
EXPLORATORY ANALYSIS

```

1
2
3  ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
4  ##
5  ## Correlation of Fixed Effects:
6  ##          (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
7  ## intrvntnbs-  0.030
8  ## intrvntnfl- -0.439 -0.476
9  ## institutin1 -0.083  0.001   -0.001
10 ## institutin2 -0.075  0.000    0.000   -0.412
11 ## expr5-10-<5  0.045 -0.001    0.000   -0.028 -0.312
12 ## exp>10-5-10  0.073  0.000    0.000    0.158  0.035 -0.442
13 ## userprtly-n  0.134  0.001    0.001   -0.292  0.200 -0.043 -0.046
14 ## usry-sprtly -0.086 -0.002    0.001   -0.374  0.134  0.001  0.007 -0.467
15
16

```

Plot - Predicted response time



Time (simple model)

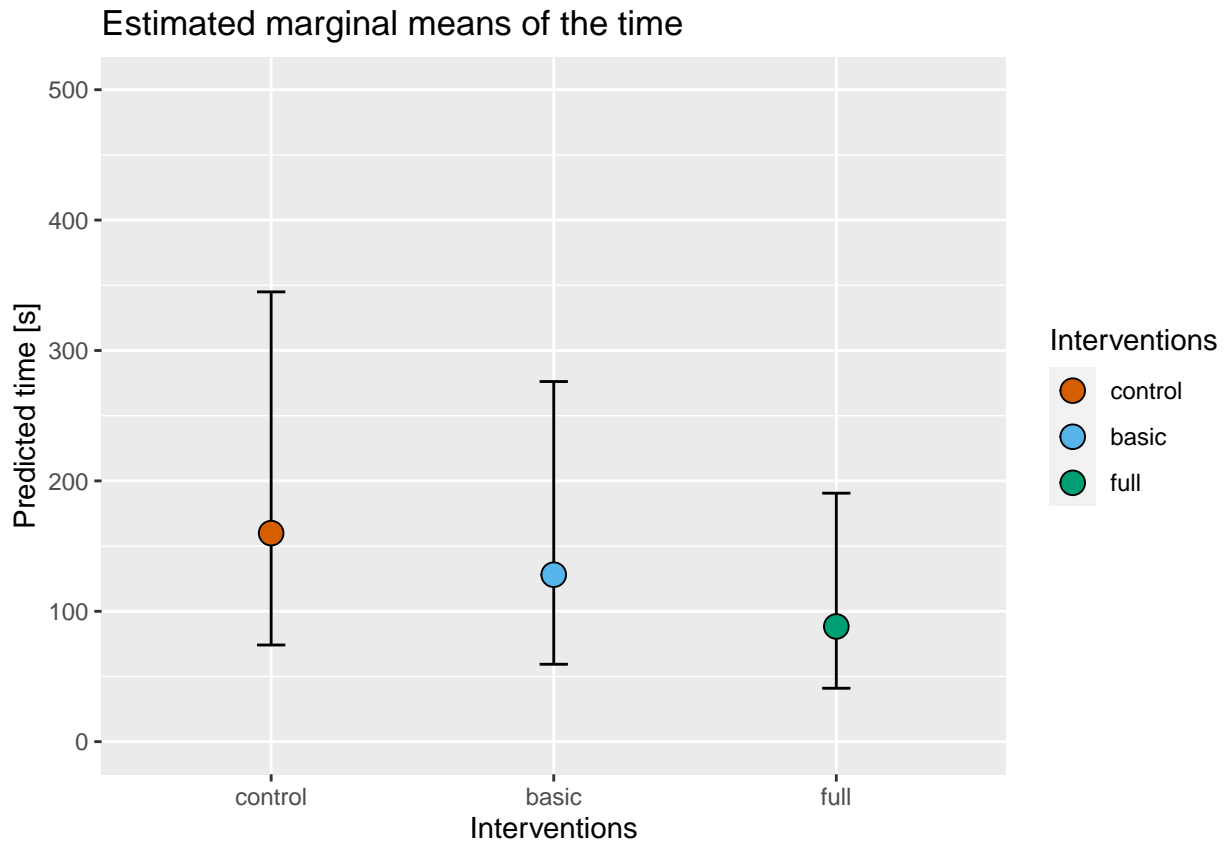
Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.93	-24.01	-15.62	<0.001
Intervention (full vs basic)	-31.01	-34.51	-27.32	<0.001

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
##
## REML criterion at convergence: 762.6
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -3.7745 -0.6461 -0.0532  0.6139  3.7661
##
## Random effects:
##   Groups   Name                Variance Std.Dev.
##   subject  (Intercept)  0.06287  0.2507
##   item     (Intercept)  0.04405  0.2099
##   Residual                    0.10814  0.3288
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error   df t value Pr(>|t|)
## (Intercept)      4.80288    0.06142 33.80208  78.194 < 2e-16 ***
## interventionbasic-control -0.22223    0.02671 861.13236  -8.319 3.45e-16 ***
## interventionfull-basic  -0.37118    0.02660 860.23224 -13.953 < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.000
## intrvntnfl-  0.001 -0.495
```


Plot - Predicted response time



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Sensitivity analysis

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0664
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Order (block 2 vs block 1)	1.14	0.71	1.83	0.5822
Order (block 3 vs block 1)	0.80	0.49	1.32	0.3783

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + block_order + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##           AIC      BIC   logLik deviance df.resid
##           708.8    742.7   -347.4    694.8     925
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0778 -0.4245 -0.3108 -0.1725  6.5485
##
## Random effects:
##  Groups Name          Variance Std.Dev.
##  subject (Intercept) 0.2403    0.4902
##  item (Intercept)    0.3724    0.6102
## Number of obs: 932, groups: subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1675     0.2493  -8.693 < 2e-16 ***
## interventionbasic-control -0.3950     0.2152  -1.835  0.0664 .
## interventionfull-basic  -1.4935     0.3173  -4.707 2.51e-06 ***
## block_order2         0.1327     0.2412   0.550  0.5822
## block_order3        -0.2238     0.2541  -0.881  0.3783
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb- intrvntnf- blk_2
## intrvntnbs-   0.049
## intrvntnfl-   0.212 -0.376
## block_ordr2  -0.497 -0.022    0.031
## block_ordr3  -0.466 -0.024    0.023    0.494
```

Contrasts

Contrast matrices for categorical variables

Intervention (exploratory)

```
##          basic-control full-basic
## control  -0.6666667 -0.3333333
## basic    0.3333333 -0.3333333
## full     0.3333333  0.6666667
```

User

```
##          partly-no yes-partly
## no      -0.6666667 -0.3333333
## partly  0.3333333 -0.3333333
## yes     0.3333333  0.6666667
```

Experience

```
##          5-10y-<5y >10y-5-10y
## <5y      -0.6666667 -0.3333333
## 5-10y    0.3333333 -0.3333333
## >10y     0.3333333  0.6666667
```

Institution

```
##          [,1] [,2]
## Children's hospital  1  0
## Hospital             0  1
## Community            -1 -1
```

1
2
3 subject;"item";"intervention";"intervention_order";"institution";"profession";"experience";"user";"time";"log
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3 50;"14";"basic";"2";"Hospital";"Pharmacist";"5-10y";"no";111.37;4.71285799140501;0
4 50;"15";"basic";"2";"Hospital";"Pharmacist";"5-10y";"no";70.57;4.25660512501274;1
5 50;"16";"full";"1";"Hospital";"Pharmacist";"5-10y";"no";117.01;4.76225940123087;0
6 50;"17";"basic";"2";"Hospital";"Pharmacist";"5-10y";"no";130.1;4.86830338551846;0
7 50;"18";"control";"3";"Hospital";"Pharmacist";"5-10y";"no";66.12;4.19147127295282;0
8 51;"1";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";426.84;6.05640923574836;0
9 51;"2";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";349.59;5.85676103925328;1
10 51;"3";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";439.39;6.08538740138475;1
11 51;"4";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";142.28;4.95779694708025;0
12 51;"5";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";68.39;4.22522661511;0
13 51;"6";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";88.12;4.47869952193414;0
14 51;"7";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";225.3;5.4174328474382;1
15 51;"8";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";221.96;5.4024971854577;1
16 51;"9";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";418.34;6.03629449902577;1
17 51;"10";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";219.51;5.39139778956405;1
18 51;"11";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";76.99;4.34367554328996;0
19 51;"12";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";81.76;4.40378812645539;0
20 51;"13";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";147.7;4.99518318953733;0
21 51;"14";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";104.61;4.65023914935567;1
22 51;"15";"basic";"1";"Hospital";"Pharmacist";"5-10y";"no";88;4.47733681447821;0
23 51;"16";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";65.25;4.1782260462028;0
24 51;"17";"full";"3";"Hospital";"Pharmacist";"5-10y";"no";59.99;4.094177881665;0
25 51;"18";"control";"2";"Hospital";"Pharmacist";"5-10y";"no";144.41;4.97265647613847;0
26 52;"1";"basic";"1";"Community";"Pharmacist";"<5y";"no";313.65;5.74827771454275;0
27 52;"2";"basic";"1";"Community";"Pharmacist";"<5y";"no";252.84;5.5327568776041;0
28 52;"3";"basic";"1";"Community";"Pharmacist";"<5y";"no";339.97;5.82885737842313;0
29 52;"4";"control";"3";"Community";"Pharmacist";"<5y";"no";148.98;5.00381206874813;0
30 52;"5";"control";"3";"Community";"Pharmacist";"<5y";"no";207.53;5.33527590753357;1
31 52;"6";"basic";"1";"Community";"Pharmacist";"<5y";"no";224.25;5.41276150093891;0
32 52;"7";"full";"2";"Community";"Pharmacist";"<5y";"no";186.07;5.22612294699955;0
33 52;"8";"control";"3";"Community";"Pharmacist";"<5y";"no";177.93;5.18139021451875;0
34 52;"9";"full";"2";"Community";"Pharmacist";"<5y";"no";142.08;4.95639027924386;0
35 52;"10";"basic";"1";"Community";"Pharmacist";"<5y";"no";263.16;5.5727622122178;0
36 52;"11";"full";"2";"Community";"Pharmacist";"<5y";"no";89.12;4.48998377617897;0
37 52;"12";"control";"3";"Community";"Pharmacist";"<5y";"no";113.37;4.73065680602951;0
38 52;"13";"full";"2";"Community";"Pharmacist";"<5y";"no";90.7;4.50755735712109;0
39 52;"14";"full";"2";"Community";"Pharmacist";"<5y";"no";109.25;4.6936388339757;0
40 52;"15";"full";"2";"Community";"Pharmacist";"<5y";"no";79.21;4.37210255347619;0
41 52;"16";"control";"3";"Community";"Pharmacist";"<5y";"no";157.84;5.06158186171436;0
42 52;"17";"control";"3";"Community";"Pharmacist";"<5y";"no";263.29;5.57325608628995;0
43 52;"18";"basic";"1";"Community";"Pharmacist";"<5y";"no";283.47;5.64710629746264;0
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g_time";"error"

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```
1
2
3 library(tidyverse)
4 library(lme4)
5 library(ggeffects)
6 library(emmeans)
7 library(lmerTest)
8
9
10 rm(list = ls())
11
12 set.seed(2345)
13
14
15 data <- read.table(file = "data.csv",
16                   header = TRUE,
17                   sep = ";",
18                   na.strings = "NA",
19                   stringsAsFactors = FALSE,
20                   fileEncoding = "UTF-8")
21
22
23
24 ##### SETTING CONTRASTS #####
25
26 # INTERVENTION
27 # subset data
28 data <- data %>% dplyr::filter(intervention != "basic")
29
30
31 data$intervention <- factor(data$intervention,
32                            levels = c("control",
33                                       "full"),
34                            ordered = TRUE)
35
36
37 contrasts(data$intervention) <- contr.treatment(levels(data$intervention))
38
39 # CLINIC
40 data$institution <- factor(x = data$institution,
41                           levels = c("Childrens hospital",
42                                       "Hospital",
43                                       "Community")
44 )
45
46
47 # Sum
48 contrasts(data$institution) <- contr.sum(levels(data$institution))
49
50 # EXPERIENCE
51 data$experience <- factor(x = data$experience,
52                          levels = c("<5y",
53                                       "5-10y",
54                                       ">10y"),
55 )
56
57
58
59
60
```



```
1
2
3         ordered = TRUE)
4 # Difference
5 contrasts(data$experience) <- MASS::contr.sdif(levels(data$experience))
6
7
8 # USER
9 data$user <- factor(x = data$user,
10                    levels = c("no",
11                               "partly",
12                               "yes"),
13                    ordered = TRUE)
14 # Difference
15 contrasts(data$user) <- MASS::contr.sdif(levels(data$user))
16
17
18
19 ##### MODELLING #####
20
21 # ERROR
22
23
24 ## FULL
25 model_error <- lme4::glmer(error ~ intervention + institution + user + (intervention | subject) +
26 (intervention | item),
27                          data = data,
28                          family = binomial(link = "logit"),
29                          glmerControl(optimizer = "bobyqa")
30 )
31
32
33
34 summary(model_error)
35
36
37 exp(lme4::confint.merMod(object = model_error,
38                          level = 0.95,
39                          method = "Wald")
40 )
41
42 ## SIMPLE
43 model_error_simple <- glmer(error ~ intervention + (1 | subject) + (1 | item),
44                             data = data,
45                             family = binomial(link = "logit"),
46                             glmerControl(optimizer = "bobyqa")
47 )
48
49
50 summary(model_error_simple)
51
52
53 exp(lme4::confint.merMod(object = model_error_simple,
54                          level = 0.95,
55                          method = "Wald")
56 )
57
58
59
60
```

```
1
2
3 )
4
5
6
7 # TIME
8 ## FULL
9 model_time <- lmerTest::lmer(log_time ~ intervention + institution + experience + user +
10 (intervention | subject) + (intervention | item),
11 data = data,
12 REML = TRUE)
13
14 summary(model_time)
15
16
17 1 - exp(lme4::confint.merMod(object = model_time,
18 level = 0.95,
19 method = "Wald")
20 )
21
22
23 ## SIMPLE
24 model_time_simple <- lmerTest::lmer(log_time ~ intervention + (1 | subject) + (1 | item),
25 data = data,
26 REML = TRUE)
27
28 summary(model_time_simple)
29
30
31 1 - exp(lme4::confint.merMod(object = model_time_simple,
32 level = 0.95,
33 method = "Wald")
34 )
35
36
37 ##### MARGINAL MEANS PLOTS #####
38
39
40 # TIME
41 ## FULL
42 emm_model_error <- ggemmeans(model_error, term = "intervention", type = "re")
43
44
45 ggplot(emm_model_error, aes(x = x,
46 y = predicted),
47 expand.grid = F) +
48 geom_errorbar(aes(ymin = conf.low,
49 ymax = conf.high),
50 width = .1) +
51 geom_point(size = 4,
52 shape = 21,
53 color = "black",
54 aes(fill = x))
55
56
57
58
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60
```

```

1
2
3   )+
4   scale_y_continuous(breaks = seq(0, 1, by = 0.2), limits = c(0, 1)
5   )+
6   scale_fill_manual(values = c("control" = "#D55E00",
7     "full" = "#009E73")
8   )+
9   labs(x = "Interventions",
10      y = "Predicted error probability",
11      fill = "Interventions") +
12   ggtitle(label = "Estimated marginal means of the interventions")
13
14
15
16
17
18 ## SIMPLE
19 emm_model_error_simple <- ggemmeans(model_error_simple,
20   terms = "intervention",
21   type = "re")
22
23
24 ggplot(emm_model_error_simple, aes(x = x,
25   y = predicted),
26   expand.grid = F) +
27   geom_errorbar(aes(ymin = conf.low,
28     ymax = conf.high),
29     width = .1) +
30   geom_point(size = 4,
31     shape = 21,
32     color = "black",
33     aes(fill = x)
34   )+
35   scale_y_continuous(breaks = seq(0, 1, by = 0.2),
36     limits = c(0, 1)
37   )+
38   scale_fill_manual(values = c("control" = "#D55E00",
39     "full" = "#009E73")
40   )+
41   labs(x = "Interventions",
42     y = "Predicted error probability",
43     fill = "Interventions") +
44   ggtitle(label = "Estimated marginal means of the interventions")
45
46
47
48
49
50 # TIME
51 ## FULL
52 emm_model_time <- ggemmeans(model_time,
53   terms = "intervention",
54   type = "re")
55
56
57
58
59
60

```

```
1
2
3
4 ggplot(emm_model_time, aes(x = x,
5 y = exp(predicted),
6 shape = group),
7 expand.grid = F) +
8 geom_errorbar(aes(ymin = exp(conf.low),
9 ymax = exp(conf.high)),
10 width = .1) +
11 geom_point(size = 4,
12 shape = 21,
13 color = "black",
14 aes(fill = x)
15 ) +
16 scale_y_continuous(breaks = seq(0, 500, by = 100),
17 limits = c(0, 500)) +
18 scale_fill_manual(values = c("control" = "#D55E00",
19 "full" = "#009E73")
20 ) +
21 labs(x = "Interventions",
22 y = "Predicted time [s]",
23 fill = "Interventions") +
24 ggtitle(label = "Estimated marginal means of the time")
25
26
27
28
29
```

```
30
31 ## SIMPLE
```

```
32 emm_model_time_simple <- ggemmeans(model_time_simple,
33 terms = "intervention",
34 type = "re")
35
```

```
36
37 ggplot(emm_model_time_simple,
38 aes(
39 x = x,
40 y = exp(predicted),
41 shape = group
42 ),
43 expand.grid = F) +
44 geom_errorbar(aes(ymin = exp(conf.low),
45 ymax = exp(conf.high)),
46 width = .1) +
47 geom_point(size = 4,
48 shape = 21,
49 color = "black",
50 aes(fill = x)
51 ) +
52 scale_y_continuous(breaks = seq(0, 500, by = 100),
53 limits = c(0, 500)) +
54
55
56
57
58
59
```

```
1
2
3 scale_fill_manual(values = c("control" = "#D55E00",
4                           "full" = "#009E73")) +
5
6 labs(x = "Interventions",
7      y = "Predicted time [s]",
8      fill = "Interventions") +
9 ggtitle(label = "Estimated marginal means of the time")
10
11
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```

Confidential: For Review Only

```
1
2
3 library(tidyverse)
4 library(lme4)
5 library(ggeffects)
6 library(emmeans)
7 library(lmerTest)
8 library(MASS)
9
10
11 rm(list = ls())
12
13 set.seed(2345)
14
15
16 data <- read.table(file = "data.csv",
17                   header = TRUE,
18                   sep = ";",
19                   na.strings = "NA",
20                   stringsAsFactors = FALSE,
21                   fileEncoding = "UTF-8")
22
23
24
25 ##### DEFINING FACTORS AND SETTING CONTRASTS #####
26
27
28 # INTERVENTION
29 data$intervention <- factor(data$intervention,
30                            levels = c("control",
31                                       "basic",
32                                       "full"),
33                            ordered = TRUE)
34
35
36 # Contrast: Difference
37 contrasts(data$intervention) <- MASS::contr.sdif(levels(data$intervention))
38
39
40 # CLINIC
41 data$institution <- factor(x = data$institution,
42                           levels = c("Childrens hospital",
43                                       "Hospital",
44                                       "Community"),
45                           ordered = FALSE)
46
47
48 # Contrast: Sum
49 contrasts(data$institution) <- contr.sum(levels(data$institution))
50
51
52 # EXPERIENCE
53 data$experience <- factor(x = data$experience,
54                           levels = c("<5y",
55                                       "5-10y",
56
57
58
59
60
```

```
1
2
3           ">10y"),
4           ordered = TRUE)
5
6
7 # Contrast: Difference
8 contrasts(data$experience) <- MASS::contr.sdif(levels(data$experience))
9
10 # USER
11 data$user <- factor(x = data$user,
12                   levels = c("no",
13                              "partly",
14                              "yes"),
15                   ordered = TRUE)
16
17
18 # Contrast: Difference
19 contrasts(data$user) <- MASS::contr.sdif(levels(data$user))
20
21
22 ##### MODELLING #####
23
24
25 # ERROR
26 ## FULL
27 emodel_error <- glmer(error ~ intervention + institution + experience + user + (1 | subject) + (1 |
28 item),
29                       data = data,
30                       family = binomial(link = "logit"),
31                       glmerControl(optimizer = "bobyqa")
32 )
33
34
35 summary(emodel_error)
36
37
38 exp(lme4::confint.merMod(object = emodel_error,
39                          level = 0.95,
40                          method = "Wald")
41 )
42
43 ## SIMPLE
44 emodel_error_simple <- glmer(error ~ intervention + (1 | subject) + (1 | item),
45                              data = data,
46                              family = binomial(link = "logit"),
47                              glmerControl(optimizer = "bobyqa")
48 )
49
50
51 summary(emodel_error_simple)
52
53
54 exp(lme4::confint.merMod(object = emodel_error_simple,
55                          level = 0.95,
```



```
1
2
3         method = "Wald")
4     )
5
6
7
8     # TIME
9     ## FULL
10    emodel_time <- lmerTest::lmer(log_time ~ intervention + institution + experience + user +
11    (intervention | subject) + (intervention | item),
12    data = data,
13    REML = TRUE)
14
15    summary(emodel_time)
16
17
18    1 - exp(lme4::confint.merMod(object = emodel_time,
19    level = 0.95,
20    method = "Wald")
21    )
22
23
24    ## SIMPLE
25    emodel_time_simple <- lmerTest::lmer(log_time ~ intervention + (1 | subject) + (1 | item),
26    data = data,
27    REML = TRUE)
28
29    summary(emodel_time_simple)
30
31
32    1 - exp(lme4::confint.merMod(object = emodel_time_simple,
33    level = 0.95,
34    method = "Wald")
35    )
36
37
38    ##### SENSITIVITY ANALYSIS #####
39
40    data_exploratory$block_order <- factor(data_exploratory$block_order,
41    levels = c(1,2,3),
42    labels = c(1,2,3),
43    ordered = TRUE)
44
45
46    contrasts(data_exploratory$block_order) <-
47    contr.treatment(levels(data_exploratory$block_order))
48
49    model_order_error <- lme4::glmer(error ~ intervention + block_order + (1 | subject) + (1 | item),
50    data = data_exploratory,
51    family = binomial(link = "logit"),
52    glmerControl(optimizer = "bobyqa")
53    )
54
55
56
57
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60
```

```
1
2
3 summary(model_order_error)
4
5
6
7 ##### MARGINAL MEANS PLOTS #####
8
9 # ERROR
10 ## FULL
11 emm_emodel_error <- ggemmeans(emodel_error,
12   term = "intervention",
13   type = "re")
14
15
16 ggplot(emm_emodel_error, aes(x = x,
17   y = predicted),
18   expand.grid = F) +
19   geom_errorbar(aes(ymin = conf.low,
20     ymax = conf.high),
21     width = .1) +
22   geom_point(size = 4,
23     shape = 21,
24     color = "black",
25     aes(fill = x)) +
26   scale_y_continuous(breaks = seq(0, 1, by = 0.2),
27     limits = c(0, 1)) +
28   scale_fill_manual(values = c("control" = "#D55E00",
29     "basic" = "#56B4E9",
30     "full" = "#009E73"))
31
32 ) +
33 labs(x = "Interventions",
34   y = "Predicted error probability",
35   fill = "Interventions") +
36 ggtitle(label = "Estimated marginal means of the interventions")
37
38
39
40
41 ## SIMPLE
42 emm_emodel_error_simple <- ggemmeans(emodel_error_simple,
43   terms = "intervention",
44   type = "re")
45
46
47 ggplot(emm_emodel_error_simple, aes(x = x,
48   y = predicted),
49   expand.grid = F) +
50   geom_errorbar(aes(ymin = conf.low,
51     ymax = conf.high),
52     width = .1) +
53   geom_point(size = 4,
54     shape = 21,
```

```
1
2
3     color = "black",
4     aes(fill = x)
5 )+
6 scale_y_continuous(breaks = seq(0, 1, by = 0.2), limits = c(0, 1)) +
7 scale_fill_manual(values = c("control" = "#D55E00",
8     "basic" = "#56B4E9",
9     "full" = "#009E73")
10 )+
11 labs(x = "Interventions",
12     y = "Predicted error probability",
13     fill = "Interventions") +
14 ggtitle(label = "Estimated marginal means of the interventions")
15
16
17
18 # TIME
19 ## FULL
20 emm_emodel_time <- ggemmeans(emodel_time,
21     terms = "intervention",
22     type = "re")
23
24
25 ggplot(emm_emodel_time, aes(x = x,
26     y = exp(predicted),
27     shape = group),
28     expand.grid = F) +
29 geom_errorbar(aes(ymin = exp(conf.low),
30     ymax = exp(conf.high)),
31     width = .1) +
32 geom_point(size = 4,
33     shape = 21,
34     color = "black",
35     aes(fill = x)
36 )+
37 scale_y_continuous(breaks = seq(0, 500, by = 100),
38     limits = c(0, 500)) +
39 scale_fill_manual(values = c("control" = "#D55E00",
40     "basic" = "#56B4E9",
41     "full" = "#009E73")
42 )+
43 labs(x = "Interventions",
44     y = "Predicted time [s]",
45     fill = "Interventions") +
46 ggtitle(label = "Estimated marginal means of the time")
47
48
49
50
51
52
53
54 ## SIMPLE
55 emm_emodel_time_simple <- ggemmeans(emodel_time_simple,
```

```
1
2
3           terms = "intervention",
4           type = "re")
5
6
7 ggplot(emm_emodel_time_simple, aes(x = x,
8           y = exp(predicted),
9           shape = group),
10        expand.grid = F) +
11 geom_errorbar(aes(ymin = exp(conf.low),
12           ymax = exp(conf.high),
13           width = .1) +
14 geom_point(size = 4,
15           shape = 21,
16           color = "black",
17           aes(fill = x)) +
18 scale_y_continuous(breaks = seq(0, 500, by = 100),
19           limits = c(0, 500)) +
20 scale_fill_manual(values = c("control" = "#D55E00",
21           "basic" = "#56B4E9",
22           "full" = "#009E73"))
23 ) +
24 labs(x = "Interventions",
25       y = "Predicted time [s]",
26       fill = "Interventions") +
27 ggtitle(label = "Estimated marginal means of the time")
28
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BMJ Paediatrics Open

Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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Manuscript ID	bmjpo-2022-001726.R2
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Title

Impact of a clinical decision support system on pediatric drug dose prescribing – a randomized within-subject simulation trial

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What is already known on this topic:

Drug dose calculation errors are a well-reported source of preventable harm in pediatrics. Clinical decision support systems (CDSS) 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 PDeDose, 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 health care providers to use them.

Abstract

Background

Drug dosing errors are among the most frequent causes of preventable harm in pediatrics. Due to the complexity of pediatric 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. HCP 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 randomized 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 HCP participated in the trial. The odds ratio for an erroneous dosage using the CDSS as compared to the SmPC with pocket calculator was 0.08 (95% CI 0.02 to 0.36, $p < .001$). Thus, the odds of an error were 12-times higher while using the SmPC. Furthermore, there was a 45% (95% CI 39% to 51%, $p < .001$) 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 pediatrics. 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.

Introduction

Background and objectives

In pediatric 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 pediatric populations and are prescribed off-label.[2,3] Additionally, developmental changes affecting the pharmacokinetics have to be considered when prescribing.[4] As a consequence, pediatric 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 pediatric 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 pediatric pharmacotherapy.[12]

PEDeDose is a CDSS to facilitate drug dosing in pediatrics.[13,14] It provides health care professionals (HCP) 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 Inc. 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 hypothesized 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 to manual calculation using a pocket calculator. To assess this, a randomized within-subject simulation trial was conducted, where HCPs were asked to calculate dosages for hypothetical but clinically relevant patient cases.

Methods

Trial design

We conducted a randomized 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 pediatric patient, was created (Supplement 1). The items were developed by the main author (LH) and reviewed by two clinical pharmacists (KK, PV) with extensive experience in the field of pediatrics and neonatology. Only drugs with a pediatric 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 visualized in Figure 1.

No ethical approval was necessary as the study did not fall within the scope of the Swiss Human Research Act. This was clarified in advance with the responsible ethics commission. We report this study in concordance with the 'Reporting Guidelines for Health Care 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 pediatric clinics, and HCPs working in the ambulatory setting i.e. 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 pediatric 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 pediatric dosing information and a built-in calculator for individualized 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

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3 defined three interventions: The Swiss SmPC used together with a pocket calculator (*control*), the CDSS
4 PEdDose (*full*), and the PEdDose dosing information used together with a pocket calculator (*basic*).
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6 The study was powered to compare the CDSS PEdDose (*full*) to the SmPC used together with a pocket
7 calculator (*control*). The SmPC is a full-text electronic resource, while the data of the PEdDose
8 database is highly structured. Thus, to isolate the effect of structuring drug dosing information, we
9 exploratorily assessed the impact of using PEdDose without the built-in calculator. An example of the
10 structured dosing information from PEdDose is shown in Supplement 2.
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15 **Simulation setup**

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17 The trial was developed using the Gorilla Experiment Builder (www.gorilla.sc), a web-based trial
18 platform.[18] We conducted the trial at the participants workplace. Depending on the availability
19 participants were using their own computers or were provided with a notebook for the trial. The Gorilla
20 website was opened in a browser while the interventions (i.e. SmPC or PEdDose websites) were
21 opened either in a different browser tab or window, depending on the participants preferences. Before
22 the trial started, every participant was briefed about the aim and the design of the trial. Subsequently,
23 the participants were required to solve a dedicated test example with the PEdDose built-in calculator
24 (*full*). This ensured that the participants fully understood the capabilities of PEdDose, such as the
25 possibility to convert the calculated dosage to the correct dosing unit (e.g. mg to mL).
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33 Participants were instructed to round the calculated dosage to a maximum of two decimal places. If a
34 dose range was provided by the respective dosing information, participants were asked to submit a
35 range as a result, too.
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39 **Outcomes**

40 The primary outcome was the correctness of the derived dosage, a binary variable with 1 = error and
41 0 = correct. The secondary outcome was the time needed to solve an item.
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45 Since the dosing information that the participants were required to use was specified in advance and
46 no additional clinical evaluation was required, there was an objectively correct dosage for every item
47 within the corresponding dosing information (SmPC or PEdDose). Errors were defined as submitted
48 responses that exceeded clinically non-relevant deviations of 5% or 10% for drugs with narrow or wide
49 therapeutic windows, respectively (Supplement 1). Even though the participants were required to
50 submit dose ranges as a range, we did not consider it an error if the submitted dosage was a single
51 dosage that was within the correct window. We reviewed all erroneous responses and tried to
52 determine the possible cause of error. For the errors that were found in the *full* block (i.e. PEdDose
53 with built-in calculator), the logging data of the PEdDose built-in calculator were additionally
54 analyzed. This allowed us to assess whether the participant had specified the calculator inputs
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3 incorrectly (i.e. drug, indication, route of administration, birthdate, weight, height, and gestational
4 age).

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7 The secondary outcome response time was defined as the time difference (in seconds) for each item
8 between the time stamp on the mouse click that initialized item loading and the click that submitted
9 the result. We defined outliers in the time outcome as values greater than three standard deviations
10 for each intervention. We removed outliers and missing values and analyzed only complete items.
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13 14 15 **Covariates**

16 The following categorical participant covariates were assessed prior to the trial start: The type of
17 institution where the participant was working as an unordered factor (children's hospital, general
18 hospital with children's clinic, public pharmacy or doctor's office), their profession (physician,
19 pharmacist), their working experience as an ordered factor (<5 years, 5-10 years, >10 years), and
20 whether they had been already using PDeDose in their daily work (yes, partly, no).
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25 26 **Sample size**

27 The sample size estimation was done in collaboration with the Clinical Trial Unit of the University of
28 Basel, Switzerland. An *a priori* error rate of 20% for the control study arm was assumed based on the
29 results of previous research estimating a 26.5% error rate for dose calculation using a pocket
30 calculator.[19] A 50% overall error reduction at a significance level of 5% with >80% power resulted in
31 a total of 600 items that need to be rated. We aimed to test the two arms for the confirmatory analysis
32 with six items per arm, which resulted in an estimated sample size of 50 participants (600 items / 12
33 items per participant = 50 participants) (Supplement 3). Adding an equal number of items for the
34 exploratory arm, the resulting total number of items that need to be rated was 900, which corresponds
35 to 18 items per participant.
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43 44 **Randomization**

45 Randomization was done on the level of the interventions and the items (Figure 1). Thus, for each
46 participant the order of the three interventions was randomized, while for each intervention six out of
47 the pool of 18 items were randomly drawn without replacement. The Gorilla Experimental Builder
48 enabled to design the randomization procedure directly into the trial, thus taking care of the
49 participant allocation.[18]
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54 55 **Statistical methods**

56 Statistical analyses were performed in R version 4.1.1.[20] The relevant functions and additional
57 packages used are denoted as *function* {package}. The only continuous variable was the secondary
58 outcome response time per item, which was transformed using the natural logarithm to achieve
59 normality of the residuals. Orthogonal sum-to-zero contrasts for the unordered factors 'institution'
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3 and 'profession' applying *contr.sum* {stats} were used. The lower-level effects were thus estimated at
4 the level of the grand mean and interpreted accordingly. We applied difference coding for the ordered
5 factors 'experience', 'PEDeDose user', and the exploratory version of the variable 'intervention' using
6 *contr.sdif* {MASS}.[21] Thus, each level of the ordered factors was compared to their previous level.
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8 The contrast coding scheme is provided in the supplement (Supplement 4).
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12 For the primary outcome 'error', we fitted a generalized linear mixed-effects model (GLMM) with a
13 logit-link function using *glmer* {lme4}.[22] The secondary outcome 'time' was assessed by fitting a
14 linear mixed-effects model (LMM) using *lmer* {lmerTest}.[23] All models were derived by starting with
15 maximal model specification based on the trial design, and then sequentially reducing model
16 complexity until a non-singular fit was achieved.[24] We started by defining by-subject and by-item
17 random intercepts and slopes (i.e. crossed-random effects) on each type of intervention. The main
18 variable 'intervention' and the additional covariates were treated as fixed variables.
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24 In exploratory analyses, we assessed the impact of structuring the dosing information by adding the
25 intervention *basic* (i.e. PEDeDose without the built-in calculator). Thus, the binary variable for the
26 intervention became an ordered three-level factor (*control, basic, full*). As a sensitivity analysis we
27 created a model that is only adjusted for the order of the interventions.
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31 For all models also an unadjusted model was built, containing only the variable 'intervention' as well
32 as only random intercepts for both subject and item, respectively. We derived Wald confidence
33 intervals. The *p*-values for the linear models were derived via Satterthwaite's degrees of freedom
34 method.[23] The estimated marginal means for the 'intervention' variable for all the models were
35 calculated using *emmeans* {emmeans}.[25] The summary outputs of the models are reported in the
36 supplement (Supplement 4).
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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 randomization order are visualized in Figure 2.

The characteristics of the participants are summarized in Table 1.

Table 1: Participant characteristics

Variable names	Number (%)
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)

Missing values and outliers

Of the total 936 items rated, there were four responses (0.4%) classified as missing, three in the *full* intervention, which were accidentally skipped and one 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 analyzed, 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 analyzed

Overall, 932 items were analyzed 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 analyzed, 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 (5%) errors for the *control*, *basic*, and *full* intervention, respectively. The median time [Q₁, Q₃] 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 generalized linear mixed-effects model with a logit-link was defined to estimate the adjusted odds ratio for dose derivation errors. The regression formula for the generalized linear mixed-effects model is shown below in R notation (I). The model included the covariates for institution and previous PDeDose 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) $error \sim intervention + institution + user (intervention | subject) + (intervention | item)$

(II) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 2: Effect of the intervention on error and time. The table shows the results of the confirmatory analyses comparing the CDSS PDeDose (*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**.

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			

Intervention full vs control	0.08	0.02 to 0.36	<.001
Institution Children's hospital	1.27	0.75 to 2.15	.382
Institution General hospital	1.12	0.74 to 1.70	.587
PEDeDose user partly vs no	0.57	0.27 to 1.29	.178
PEDeDose user yes vs partly	0.88	0.37 to 2.11	.771
Unadjusted model			
Intervention full vs control	0.15	0.08 to 0.27	<.001
Time			
	Time change (%)	95% Confidence interval	<i>p</i> -value
Multivariable model			
Intervention full vs control	-45	-51 to -39	<.001
Institution Children's hospital	-18	-26 to -8	<.001
Institution General hospital	3	-6 to 12	.585
Experience 5-10 y vs <5 y	3	-11 to 18	.722
Experience >10 y vs 5-10 y	1	-16 to 15	.862
PEDeDose user partly vs no	6	-9 to 26	.472
PEDeDose user yes vs partly	-8	-22 to 9	.357
Unadjusted model			
Intervention Full vs control	-45	-48 to -42	<.001

Ancillary analyses

Exploratory analyses

Additionally, we explored the impact of using structured dosing information while using a pocket calculator. The model formula of the generalized 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 to 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 (Supplement 4).

(III) $error \sim intervention + institution + user + (1 | subject) + (1 | item)$

(IV) $log(time) \sim intervention + institution + experience + user + (intervention | subject) + (intervention | item)$

Additional results of the models are reported in Supplement 4.

Table 3: Effect of the interventions on error and time. 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**.”

Errors			
	Odds ratio	95% Confidence interval	p-value
Multivariable model			
Intervention basic vs control	0.67	0.44 to 1.03	.068
Intervention full vs basic	0.22	0.12 to 0.42	<.001
Institution Children's hospital	1.37	0.9 to 2.08	.143
Institution General hospital	0.97	0.68 to 1.38	.860
Experience 5-10 y vs <5 y	1.36	0.79 to 2.36	.273
Experience >10 y vs 5-10 y	1.15	0.64 to 2.05	.644

PEDeDose user partly vs no	0.51	0.26 to 1.00	.050
PEDeDose user yes vs partly	1.33	0.68 to 2.62	.402
Unadjusted model			
Intervention basic vs control	0.67	0.44 to 1.02	.063
Intervention Full vs basic	0.22	0.12 to 0.41	<.001
Time			
	Time change (%)	95% Confidence interval	<i>p</i> -value
Multivariable model			
Intervention basic vs control	-20	-27 to -12	<.001
Intervention full vs basic	-31	-38 to -23	<.001
Institution Children's hospital	-18	-26 to -10	<.001
Institution General hospital	3	-6 to 12	.545
Experience 5-10 y vs < 5 y	2	-11 to 17	.793
Experience >10 y vs 5-10 y	-2	-16 to 13	.749
PEDeDose user partly vs no	-1	-15 to 16	.913
PEDeDose user yes vs partly	-6	-20 to 10	.467
Unadjusted model			
Intervention basic vs control	-20	-24 to -16	<.001
Intervention full vs basic	-31	-35 to -27	<.001

Analysis of error types

For each error that occurred, we assumed the most plausible error type. The logging data of the PDeDose 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.

Table 4: Assumed error types identified based on the participants' response. Column values exceed the total error count when multiple error types were identified. The categories correspond to the CDSS PDeDose (*full*), PDeDose dosing information with a pocket calculator (*basic*), and the SmPC with a pocket calculator (*control*)

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 vs 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

N/A = error type not possible or not identifiable for this intervention.

*e.g. dosage was not converted to the dispensing unit

**e.g. the loading dose was used instead of the maintenance dose

Discussion

In this simulation trial, we showed that the CDSS PEdDose (*full*) significantly reduced the number of dose calculation errors and was more efficient when compared to either the structured PEdDose 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. Randomization 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 (e.g. 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 (e.g. dose adjustments due to renal insufficiency, comorbidities, or drug-drug interactions). However in this study, the impact of the CDSS PEdDose 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 pediatric label could be created. In pediatric 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.

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 PEdDose significantly improved the error rate as compared to the SmPC by reducing the odds of an error by a factor of 12. Furthermore, the CDSS PEdDose 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 (i.e. fixed effects) had a negligible impact on both outcomes. In contrast, there was high variability between participants and items, (i.e. random effects) leading to broad confidence intervals, especially in the two blocks using pocket calculator. However, the variability was drastically reduced when the CDSS PEdDose is used. This demonstrates that the CDSS PEdDose was able to mitigate the uncertainty produced by the human factor, while other factors such as experience do not suffice. Thus, the CDSS PEdDose increased the overall safety of the individually calculated dosages in our simulation. Furthermore, since there were no noteworthy differences between frequent PEdDose users, infrequent users, and new users, we could demonstrate that the usability of the CDSS PEdDose 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 PEdDose with pocket calculator and the CDSS PEdDose was still striking with five-fold 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 PEdDose as the built-in calculator does respect the maximum dose. This again highlights the importance of providing HCPs with individualized 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 PEdDose logging data revealed that most of the errors committed with the CDSS PEdDose could be prevented with a reasonable integration into the prescribing software, such as wrong birthdate entries or transcription errors.

Generalizability

Based on the strong results and the inevitability of human errors, we are confident that the use of the CDSS PEdDose will generally enhance the safety of prescribed dosages in practice. Furthermore, the time reduction that is achieved with the use of the CDSS PEdDose 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 PEdDose. This is in contrast to real-world studies where the magnitude of the measured effect

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3 will be modified by the way the CDSS is integrated into a primary software (i.e. a clinical information
4 system), CDSS uptake (i.e. percentage of CDSS use),[27] vigilant HCPs,[11,28] or by other measures
5 implemented to prevent such types of errors. These factors might influence the effect in different
6 ways. A bad integration of the CDSS in a clinical information system will compromise usability, uptake,
7 and can enable additional types of errors to occur. On the other hand, a good integration will simply
8 rule out even more types of errors by design (e.g. transcription errors). Interestingly, clinical
9 information system providers do not need to conduct usability tests as compared to European medical
10 device manufacturers.[29,30] Last but not least, we think that it is undisputable that we should prevent
11 the occurrence of an error in the first place by using a dose calculator rather than to rely on post-hoc
12 measures or on the commendable vigilance of the HCPs.[10,11,28]

21 **Comparison with literature**

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

50 **Conclusion and outlook**

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

Confidential: For Review Only

Other information

Data availability

The data and the R scripts for the statistical analysis are available at <https://osf.io/k86j4/>.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Contributorship Statement

LH wrote the manuscript and collected the data. PV was leading the project. LH, RS, and PV designed the study. LH and RS analyzed the data. PV, RS, KK, MW, and MG reviewed the manuscript.

Conflicts of interest

LH as a PhD student is funded by PEDeus Ltd. LH, KK, MW and PV are employees of PEDeus Ltd. MG is a member of the board of directors of PEDeus Ltd as well as the medical director of the University Children's Hospital Zurich. None of the authors has any ownership in either institution. The PEDeus Ltd. is a 100% subsidiary company of the University Children's Hospital Zurich. The authors have no additional conflicts of interest to declare that are relevant to the content of this article.

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Figures

Figure 1: Visualization 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 Summary of Product Characteristics used together with a pocket calculator (control)

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 Summary of Product Characteristics with pocket calculator (control).

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 Summary of Product Characteristics with pocket calculator (control).

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 Summary of Product Characteristics with pocket calculator (control).

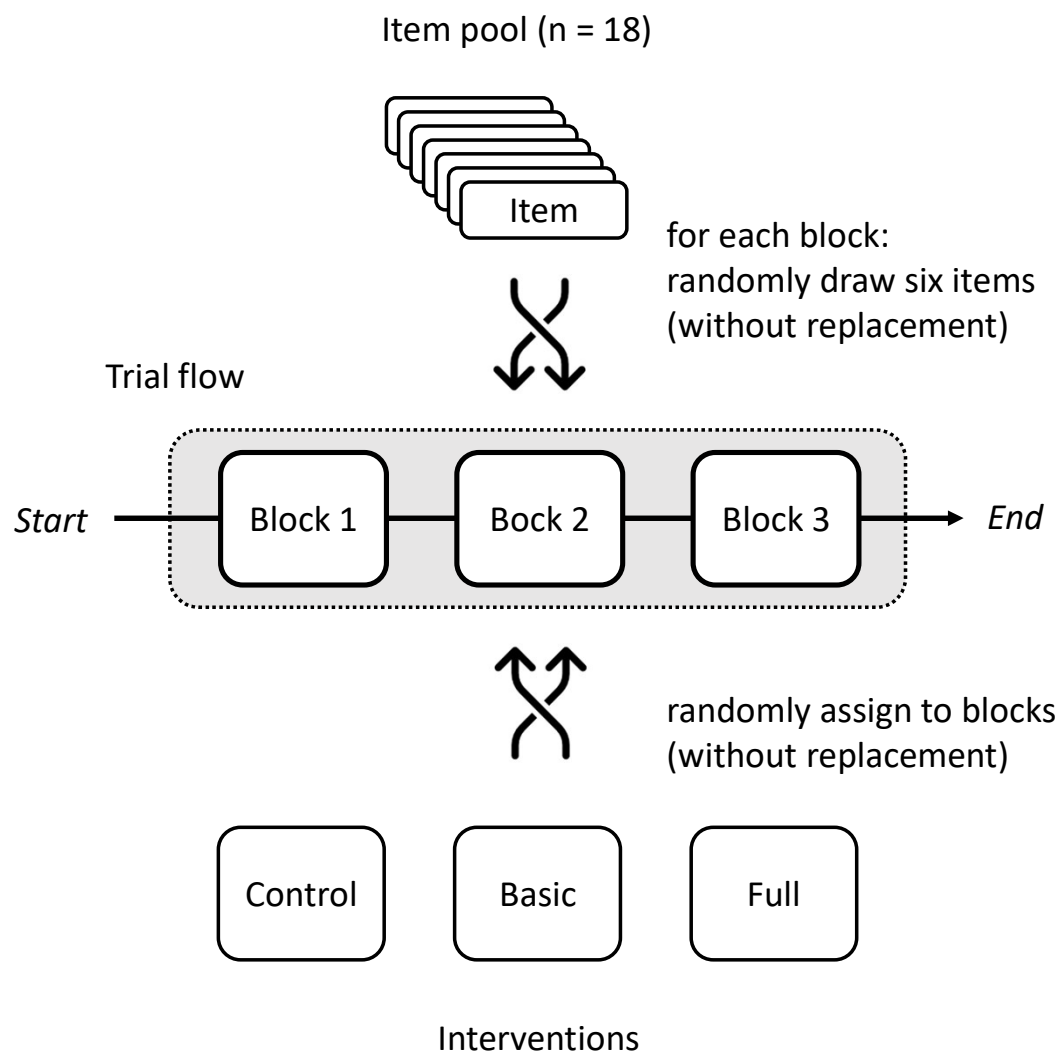
Figure 5: Number of errors stratified by intervention order and type. The name of the interventions correspond to the CDSS PEdeDose with built-in calculator (full), PEdeDose used together with a pocket calculator (basic), and Summary of Product Characteristics with pocket calculator (control).

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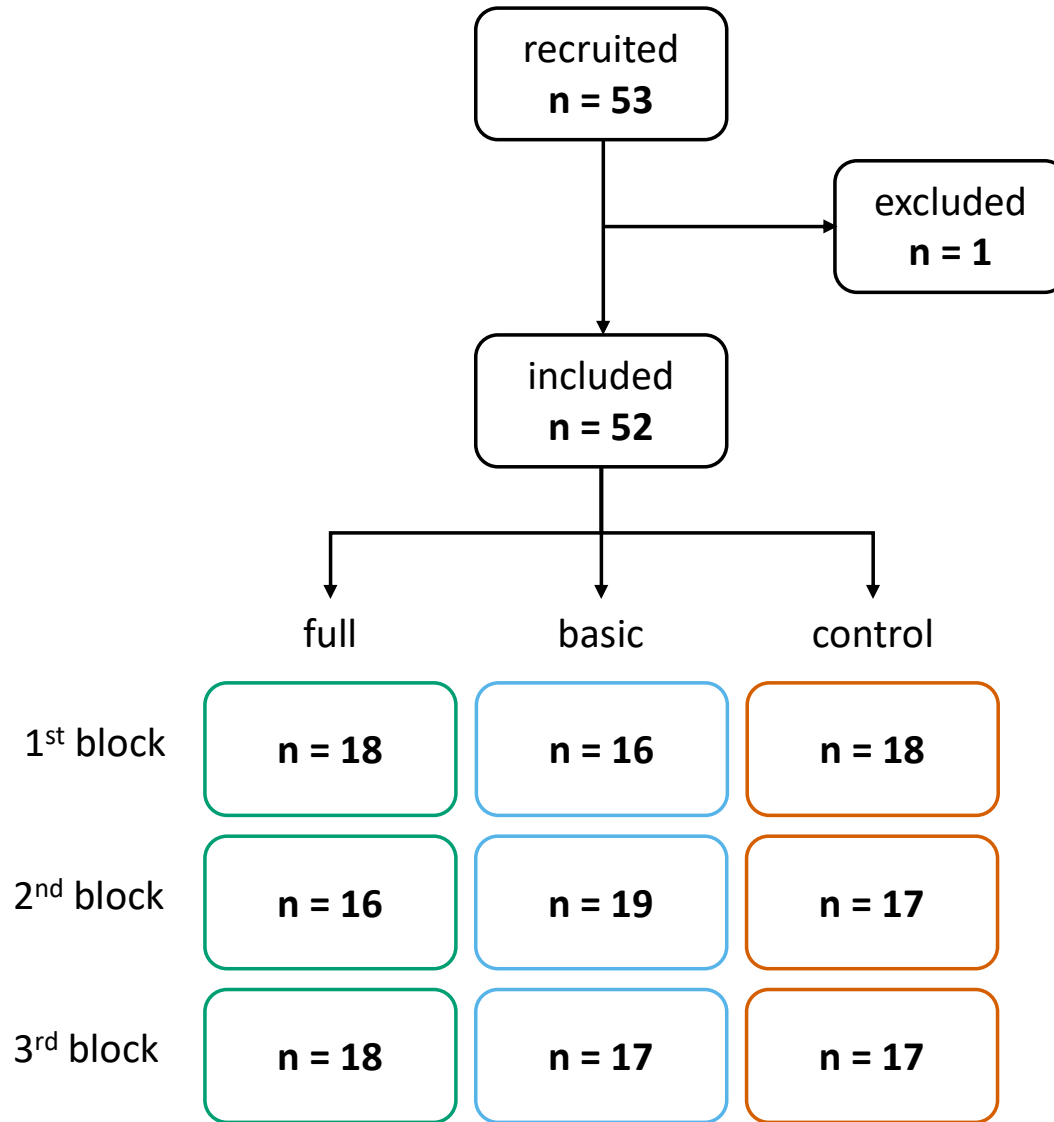
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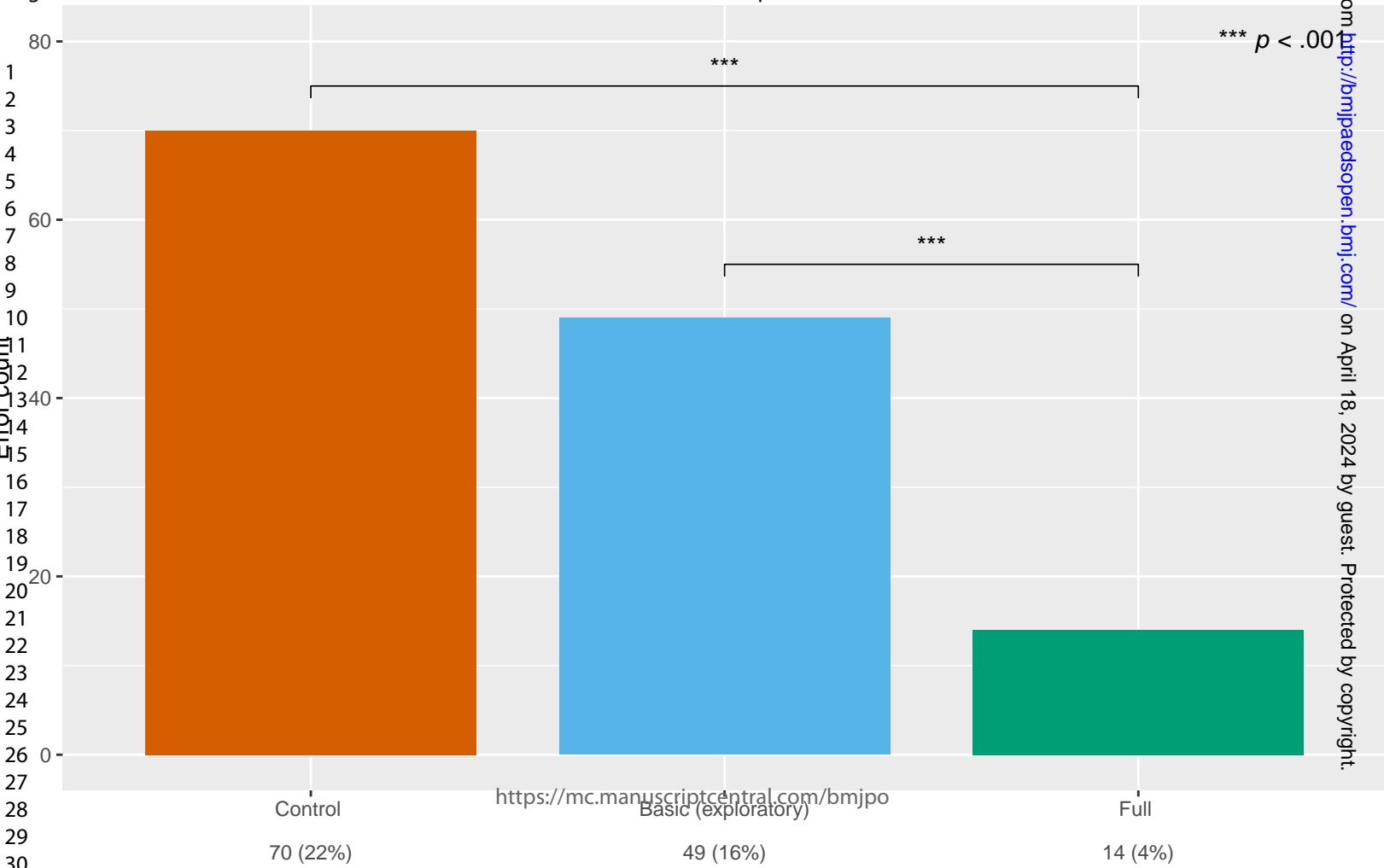


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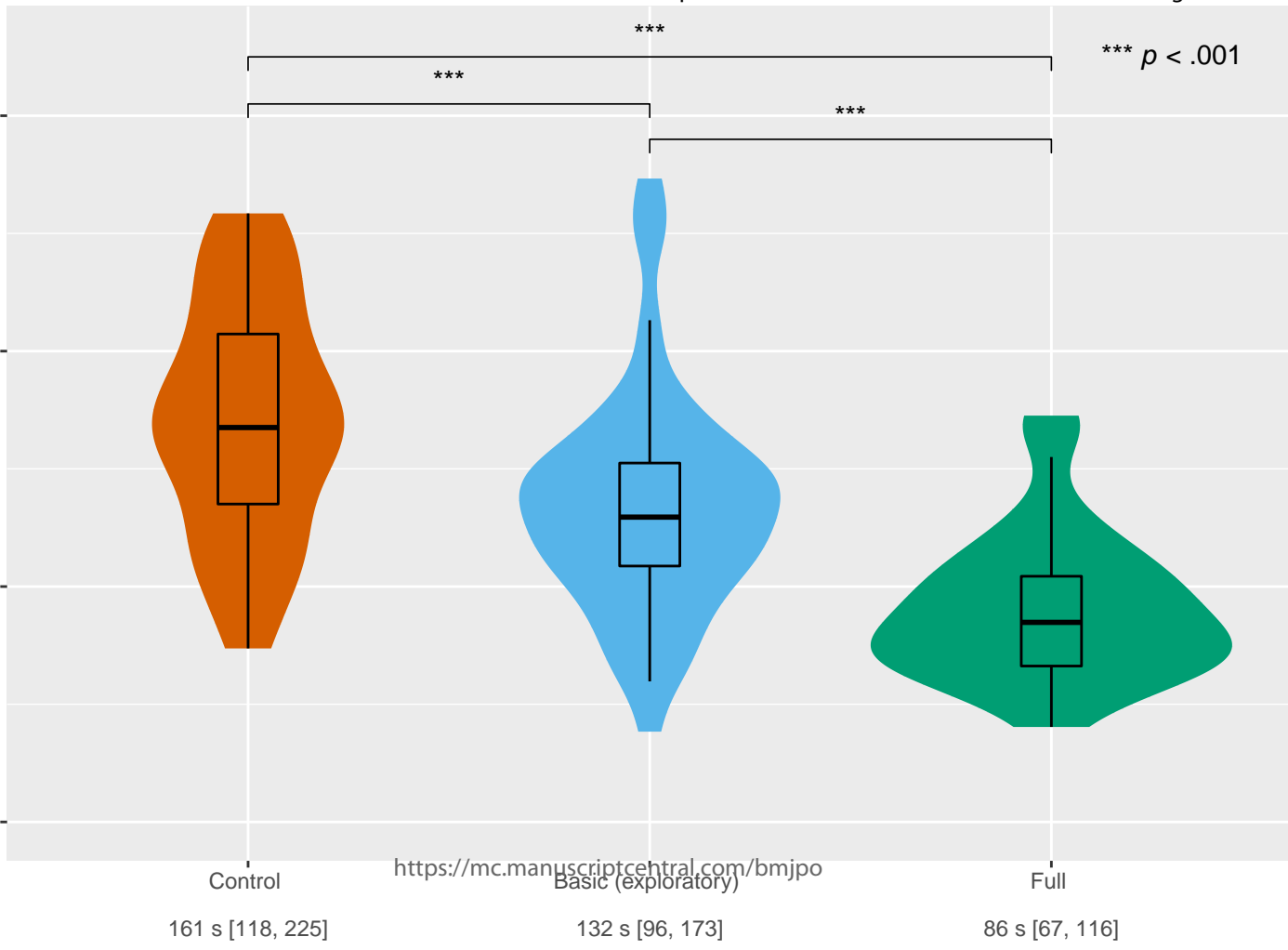
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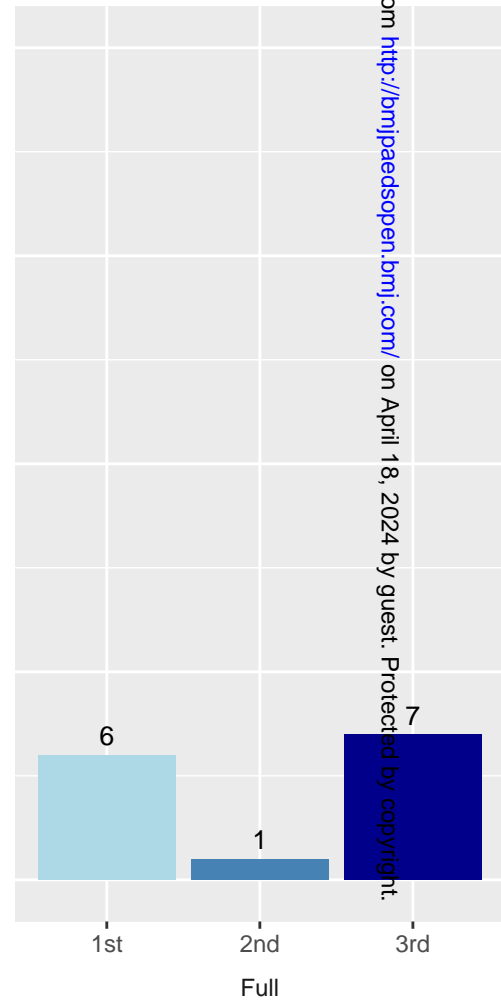
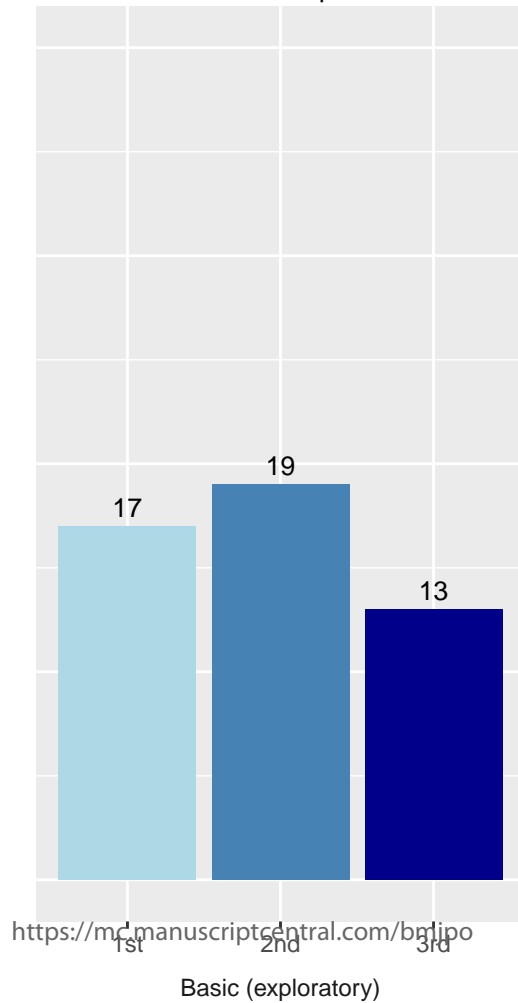
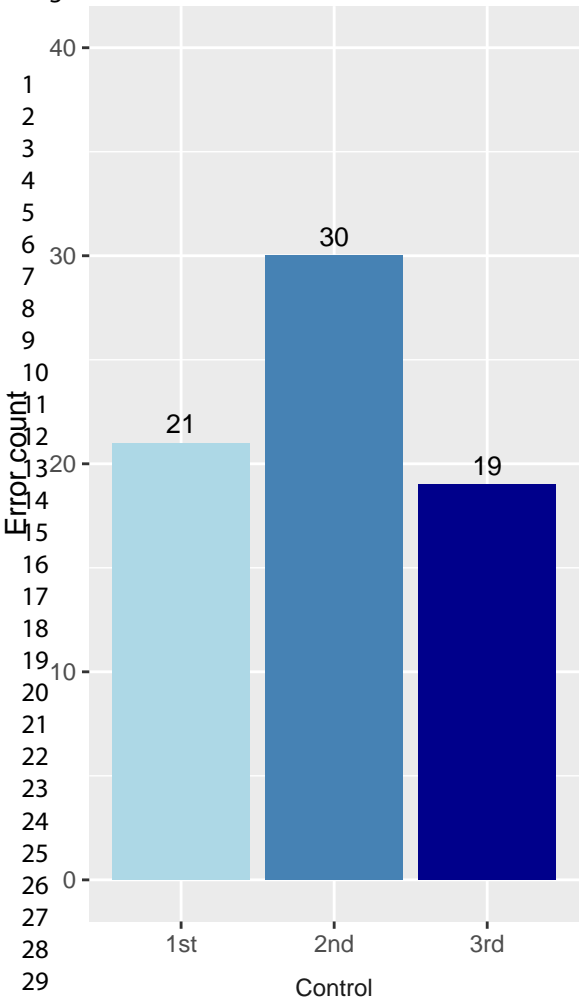
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Number of errors startified by intervention and by order

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Supplement 1 – Description of items

ID	Dosing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
1	mL/dose	infection in cystic fibrosis patients	Ciprofloxacin	p.o. (liquid)	-	2x daily	6y 10mth	26	-	no
2	mg/dose	bacterial infection (severe)	Vancomycin	i.v.	-	4x daily	5wks ^d	4.18	-	yes – GA 35 2/7
3	drops/dose	epilepsy	Clonazepam ^b	p.o. (liquid)	loading dose / begin	3x daily	6y 7mth	29	-	no
4	mL/dose	acute otitis media	Amoxicillin – Clavulanic acid	p.o. (liquid)	-	2x daily	2y 8mth	14	-	no
5	mL/dose	candidiasis (systemic)	Fluconazole	p.o. (liquid)	-	1x daily	8y	31	-	no
6	mg/dose	bacterial infection (severe)	Flucloxacillin	i.v.	-	3x daily	6d	3.2	-	no

ID	Dispensing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
7	mg/dose	nausea and vomiting in chemotherapy	Dexamethasone dihydrogen phosphate disodium	i.v.	-	4x daily	1y 6mth	12	81	no
8	mg/dose	arthritis	Methotrexate ^b	s.c.	-	1x weekly	12y 5mth	36	138	no
9	mL/dose	prophylaxis of acute rejection in patients with allogenic kidney transplantation (in combination with ciclosporin and corticosteroids)	Mycophenolate mofetil ^b	p.o. (liquid)	-	2x daily	9y 3mth	32	122	no
10	mg/dose	fungal infection (invasive)	Caspofungin	i.v.	loading dose / begin	-	11mth	9.5	76	no
11	mL/dose	bacterial infection	Clarithromycin	p.o. (liquid)	-	2x daily	7mth	7.6	-	no
12	mg/dose	tuberculosis	Isoniazid	p.o.	-	1x daily	10y 7mth	38	-	no

ID	Dispensing unit	Indication	Active ingredient	Route of administration	Dose type	Frequency	Age ^a	Weight [kg]	Height [cm]	Preterm
13	mL/dose	nausea and vomiting in chemotherapy	Ondansetron	p.o. (liquid)	follow-up treatment	3x daily	14y 10mth	46	BSA ^c : >1.2 m ²	no
14	mg/dose	bacterial infection	Ceftriaxone	i.m.	-	1x daily	5wks ^d	3.82	-	yes – GA 36 5/7
15	mL/dose	pruritus	Hydroxyzine dihydrochloride	p.o. (liquid)	-	3x daily	5y 4mth	24	-	no
16	mg/dose	intoxication with benzodiazepines	Flumazenil	i.v.	loading dose / begin	-	8y 6mth	36	-	no
17	mL/dose	insomnia	Chloral hydrate	p.o. (liquid)	-	1x daily	5y 1mth	22	-	no
18	mg/dose	urolithiasis (urates / urinary stones)	Allopurinol	p.o.	-	1x daily	13y 1mth	42	-	no

^a Age was shown to participants as birthdate calculated on the day of the experiment

^b Substance with narrow therapeutic window

^c BSA = body surface area (for this item the BSA was provided for the SmPC user as the dosing information differentiated between BSA >1.2 m² or <1.2 m²)

^d corrected age

Supplement 2 – Example of the structured dosing information of PEdeDose

Substance		Vancomycin									
Indication		bacterial infection, severe									
Route of administration		IV, parenteral									
Calculated dose											
Age	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
5 wk	4.18 kg		IV		63 mg/dose	4 x daily			by inf	B	
Date of birth 03.08.2022		Weight 4.18 kg		PI Yes		GA 35 2/7 WOP		corrA 5 wk		PNA 10 wk	
You must enter the height to be able to calculate the BMI.											
Products in Switzerland matching the data set of the calculated dose											
General doses											
Age/PMA	Weight	PI	Application	Type of dose	Dose	Number of repetitions	Max individual dose	Max daily dose	Remarks	GR	Ref
< 30 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 24 h after the loading dose; by inf	D	
< 30 wk		PI	IV	maintenance	20 mg/kg/dose	1 x daily			first maintenance dose 24 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 18 h after the loading dose; by inf	D	
30 wk - 34 wk		PI	IV	maintenance	20 mg/kg/dose	every 18 h			first maintenance dose 18 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 12 h after the loading dose; by inf	D	
34 wk - 38 wk		PI	IV	maintenance	20 mg/kg/dose	2 x daily			first maintenance dose 12 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
38 wk - 40 wk		PI	IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	loading dose	25 mg/kg/dose				as a single dose, start the maintenance dosage 8 h after the loading dose; by inf	D	
0 D - 28 D			IV	maintenance	15 mg/kg/dose	3 x daily			first maintenance dose 8 h after the loading dose; by inf	(A)	
28 D - 18 Y and < 66 kg			IV		15 mg/kg/dose	4 x daily			by inf	B	
< 18 Y and ≥ 66 kg			IV		1000 mg/dose	4 x daily			by inf	B	

Figure: Example of the vancomycin dosage information for severe bacterial infection to be administered intravenously. In the calculated dosage tab one can see the calculated dosage for a hypothetical preterm of 5 weeks of age (corrected age) with a weight of 4.18 kg analogous to item number 2 of the trial. In the general doses tab the basic dosing information can be seen.

Supplement 3 – Sample size estimation

Expected power for significant improvement of the CDSS PEDeDose vs no CDSS

Error rate without CDSS: 20%

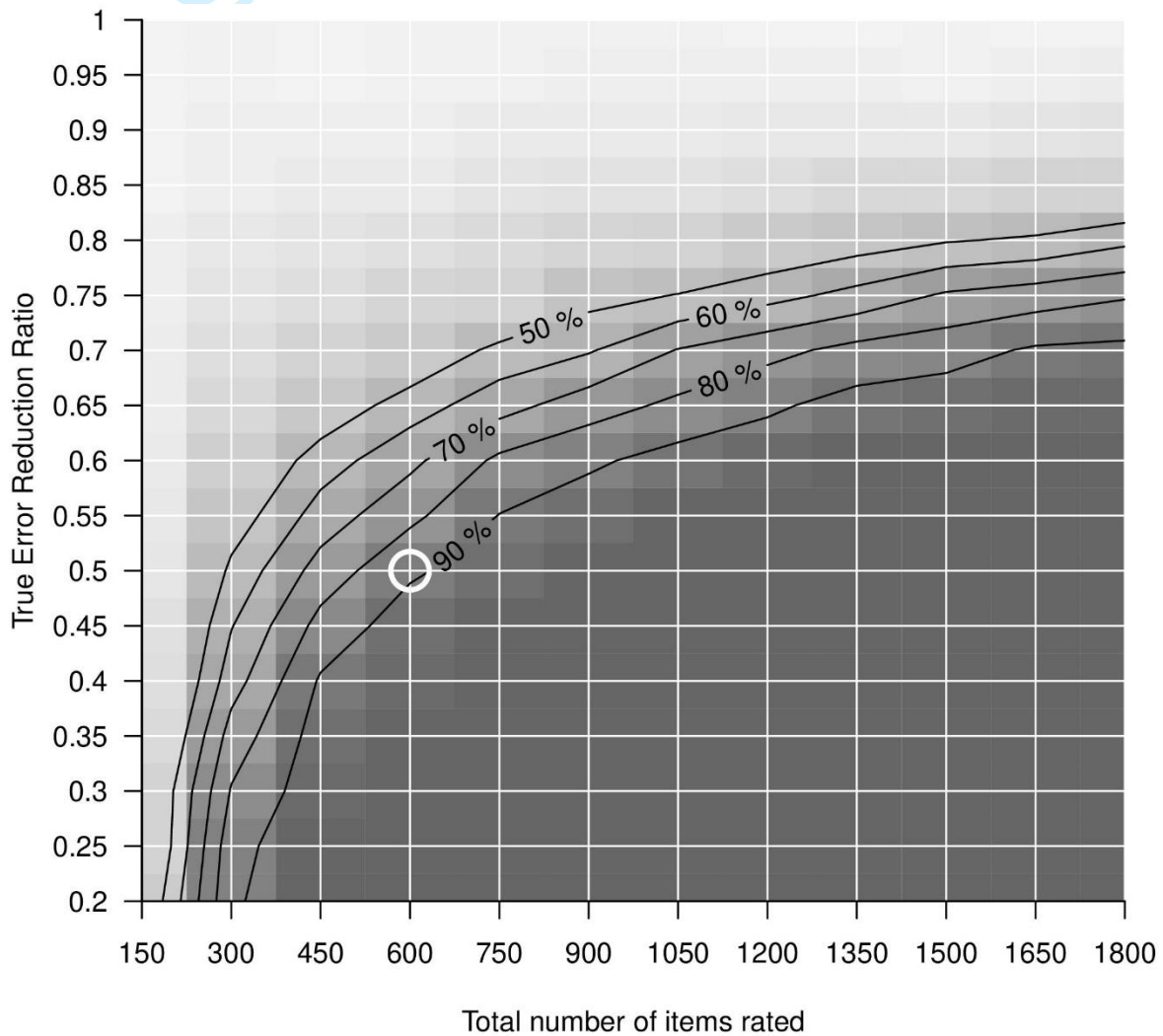


Figure: The experiment was simulated 999 times assuming between 150 to 1800 items that are rated, while achieving an error reduction ratio between 0.2 to 1 (no reduction). The white circle marks the estimated number of items that need to be rated to achieve a 50% error reduction.

Supplement 4 - Statistical analyses

Contents

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Confirmatory analysis

Errors (full model)

Results

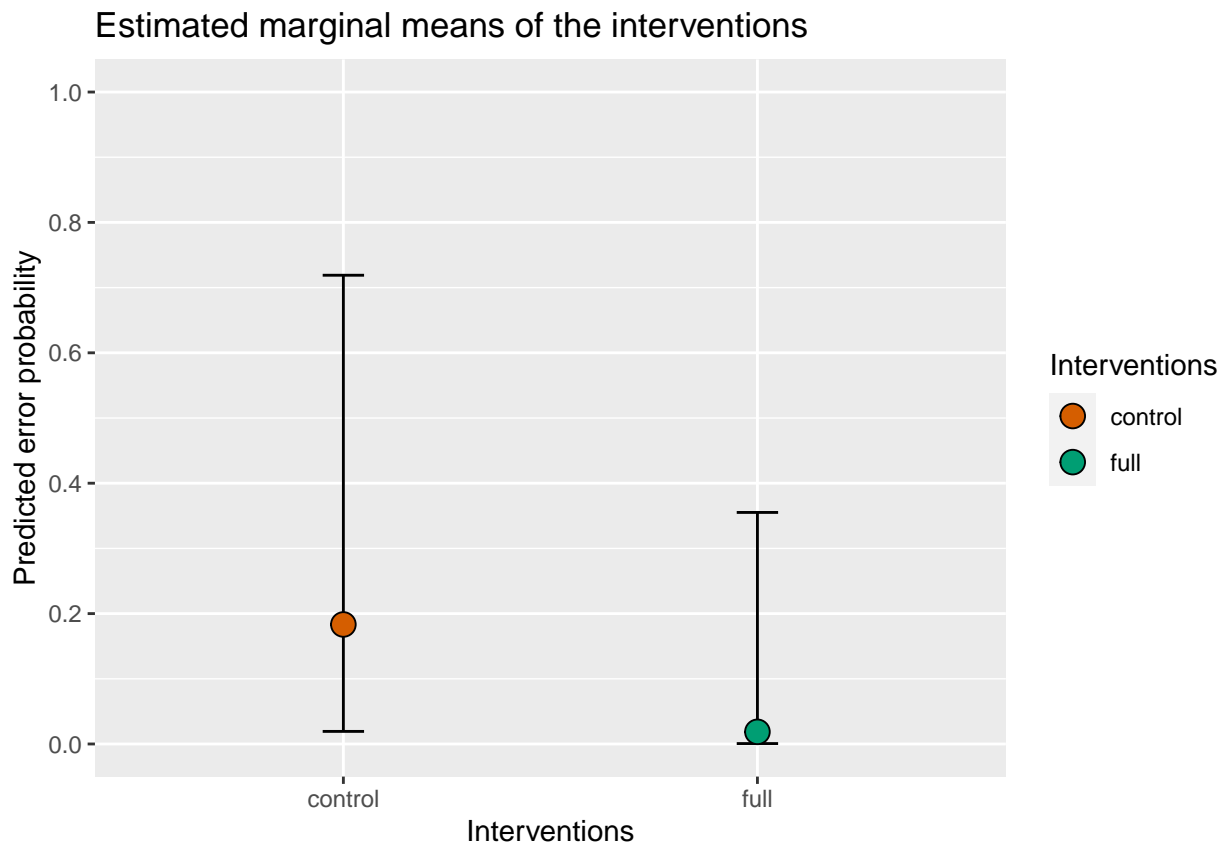
Variable	OR	CI (low)	CI (high)	p value
Intervention	0.08	0.02	0.36	<0.001
Institution (Children's hospital)	1.27	0.75	2.15	0.3823
Institution (Hospital)	1.12	0.74	1.70	0.5875
User (partly vs no)	0.57	0.26	1.29	0.1779
User (yes vs partly)	0.88	0.37	2.11	0.7712

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula:
## error ~ intervention + institution + user + (intervention | subject) +
## (intervention | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC    logLik deviance df.resid
##  457.2   510.4   -216.6   433.2     608
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8811 -0.4334 -0.2101 -0.1185  3.7005
##
## Random effects:
##      Groups Name              Variance Std.Dev. Corr
##      subject (Intercept)      0.2340   0.4838
##      interventionfull 1.4835   1.2180  -0.51
##      item (Intercept)         0.2954   0.5435
##      interventionfull 0.7559   0.8694  -0.35
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -1.4938    0.2415  -6.187 6.15e-10 ***
## interventionfull -2.4694    0.7395  -3.339 0.000839 ***
## institution1     0.2359    0.2700   0.874 0.382263
## institution2     0.1151    0.2121   0.543 0.587464
## userpartly-no   -0.5563    0.4129  -1.347 0.177867
## useryes-partly  -0.1302    0.4478  -0.291 0.771219
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
```

```
##          (Intr) intrvn instt1 instt2 usrpr-  
## intrvntnfl1 -0.252  
## institutin1 -0.139 -0.091  
## institutin2 -0.137  0.034 -0.404  
## userprtly-n  0.238  0.040 -0.297  0.165  
## usry-sprtly -0.129  0.144 -0.390  0.164 -0.467
```

Plot - Predicted probability of error



W Only

Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention	0.15	0.08	0.27	<0.001

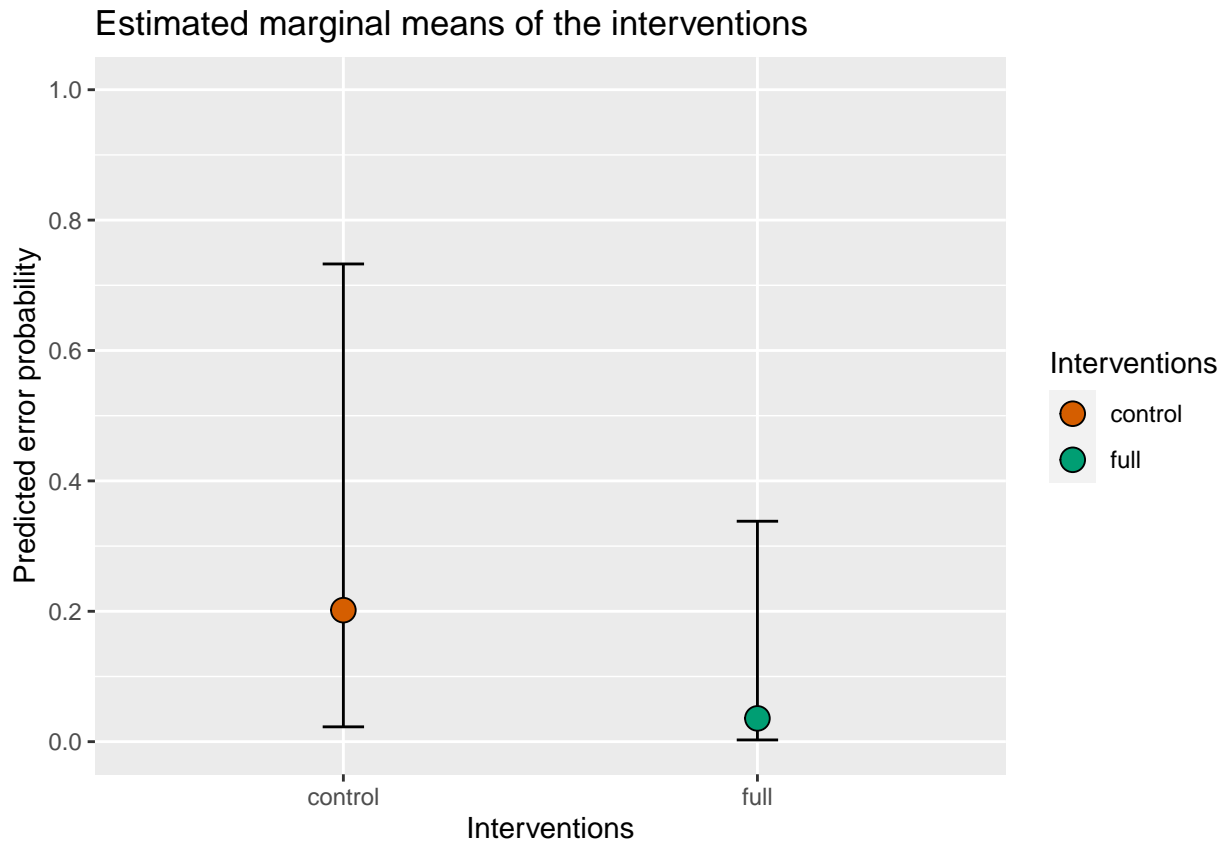
R summary output

```

## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
## Control: glmerControl(optimizer = "bobyqa")
##
##           AIC      BIC   logLik deviance df.resid
##      447.0    464.8  -219.5   439.0     616
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.8104 -0.4473 -0.2367 -0.1683  5.8528
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2236   0.4728
##  item    (Intercept) 0.2925   0.5408
## Number of obs: 620, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)    -1.3756    0.2165  -6.355 2.09e-10 ***
## interventionfull -1.9200    0.3183  -6.032 1.62e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.242

```

Plot - Predicted probability of error



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Time (full model)

Results

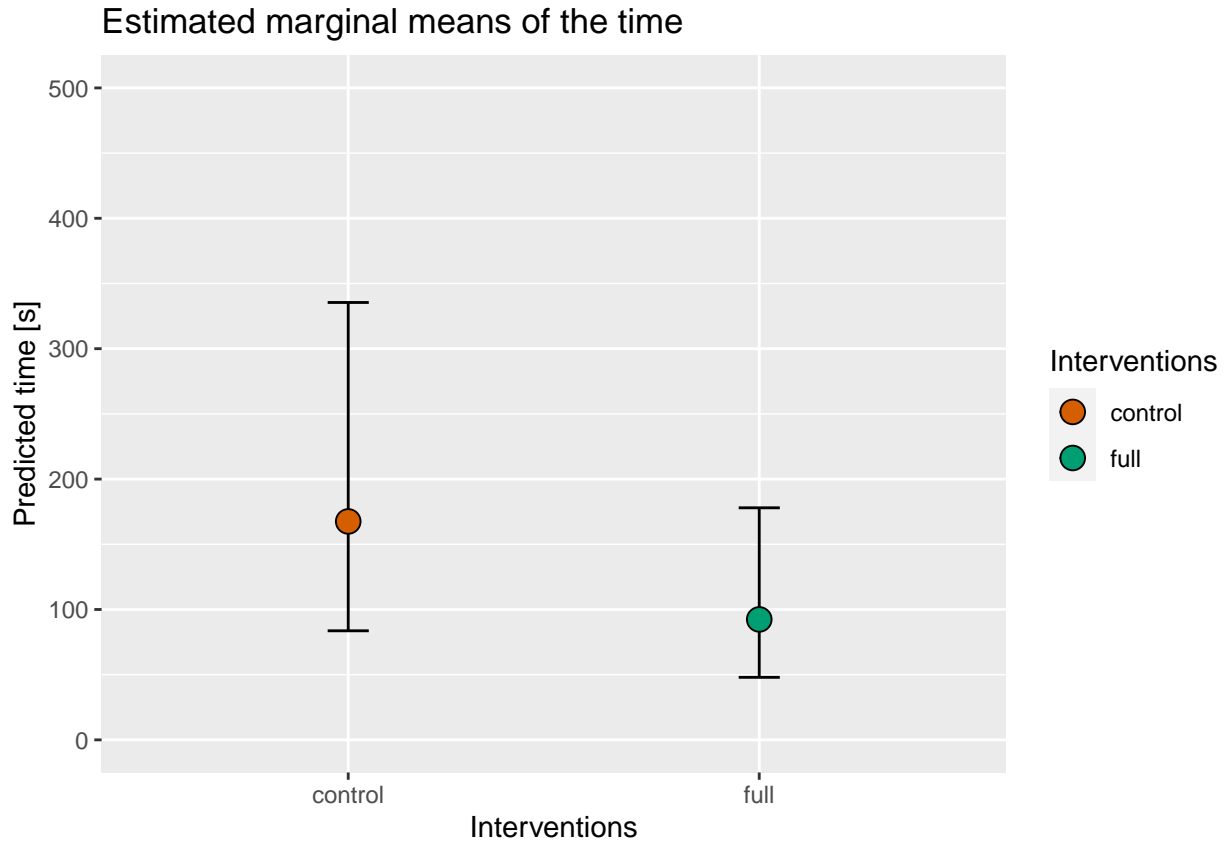
Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-44.85	-50.51	-38.54	<0.001
Institution (Children’s hospital)	-17.78	-26.16	-8.46	<0.001
Institution (Hospital)	2.60	-6.37	12.42	0.5853
Experience (5-10y vs <5y)	2.64	-10.99	18.36	0.7217
Experience (>10y vs 5-10y)	-1.39	-15.75	15.40	0.8619
User (partly vs no)	6.34	-9.92	25.52	0.4717
User (yes vs partly)	-7.73	-22.11	9.30	0.3568

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_confirmatory
##
## REML criterion at convergence: 432.7
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -3.4708 -0.6145 -0.0595  0.5344  3.1635
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject  (Intercept)          0.04406  0.2099
##           interventionfull  0.05292  0.2300  -0.35
##   item     (Intercept)          0.06619  0.2573
##           interventionfull  0.02677  0.1636  -0.91
## Residual                    0.08039  0.2835
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    5.12111    0.07072 26.21325  72.415 < 2e-16 ***
## interventionfull -0.59507    0.05524 30.37710 -10.773 6.74e-12 ***
## institution1    -0.19580    0.05480 44.96048  -3.573 0.000856 ***
## institution2     0.02564    0.04665 44.84160   0.550 0.585265
## experience5-10y-<5y  0.02606    0.07269 44.77178   0.359 0.721652
## experience>10y-5-10y -0.01404    0.08025 44.96372  -0.175 0.861888
## userpartly-no     0.06144    0.08463 44.84683   0.726 0.471654
## useryes-partly    -0.08049    0.08645 45.06018  -0.931 0.356777
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##           (Intr) intrvn instt1 instt2 e5-10- e>10-5 usrpr-
```

```
## intrvntnfl1 -0.698
## institutin1 -0.071 -0.001
## institutin2 -0.064 0.000 -0.412
## expr5-10-<5 0.039 -0.002 -0.027 -0.311
## exp>10-5-10 0.062 0.000 0.159 0.035 -0.442
## userprtly-n 0.114 0.002 -0.292 0.199 -0.043 -0.047
## usrys-prtly -0.073 -0.001 -0.375 0.134 0.000 0.007 -0.466
```

Plot - Predicted response time



Time (simple model)

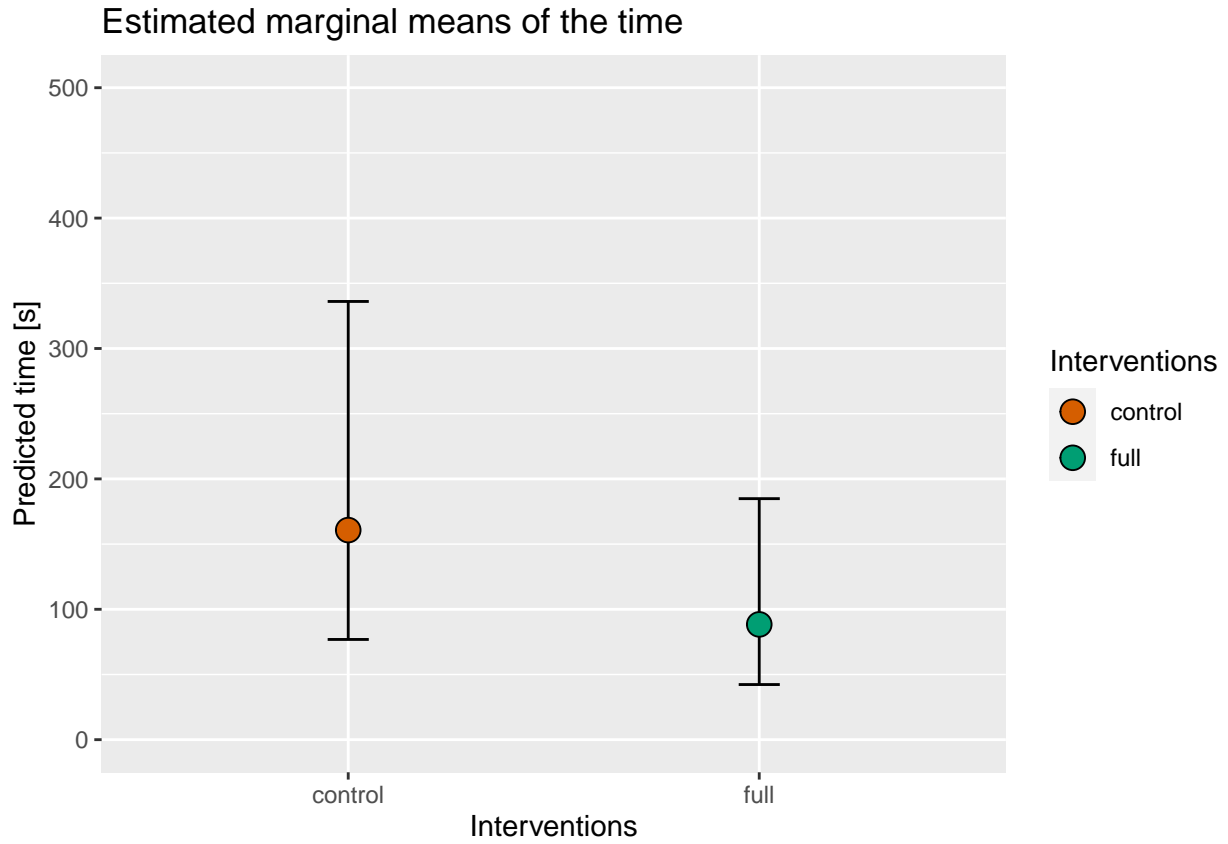
Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention	-45	-47.73	-42.12	<0.001

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_confirmatory
##
## REML criterion at convergence: 494.8
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -4.0767 -0.6149 -0.0248  0.5679  3.3763
##
## Random effects:
##   Groups   Name                Variance Std.Dev.
## subject  (Intercept)  0.05797  0.2408
## item     (Intercept)  0.03607  0.1899
## Residual                    0.10085  0.3176
## Number of obs: 618, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    5.07975    0.05877 38.59148   86.44 <2e-16 ***
## interventionfull -0.59777    0.02604 551.44043  -22.95 <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr)
## intrvntnfl1 -0.222
```

Plot - Predicted response time



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Exploratory analysis

Errors (full model)

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0677
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Institution (Children's hospital)	1.37	0.90	2.08	0.1428
Institution (Hospital)	0.97	0.68	1.38	0.8601
Experience (5-10y vs <5y)	1.36	0.79	2.36	0.2725
Experience (>10y vs 5-10y)	1.15	0.64	2.05	0.6443
User (partly vs no)	0.51	0.26	1.00	0.0498
User (yes vs partly)	1.33	0.68	2.62	0.4019

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + institution + experience + user + (1 |
## subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC   logLik deviance df.resid
##    711.6    764.9   -344.8   689.6     921
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0078 -0.4323 -0.2991 -0.1736  6.2086
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.1555   0.3943
##  item    (Intercept) 0.3354   0.5791
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.26943    0.21046 -10.783 < 2e-16 ***
## interventionbasic-control -0.39394    0.21565  -1.827  0.0677 .
## interventionfull-basic   -1.49297    0.31775  -4.699 2.62e-06 ***
## institution1           0.31265    0.21334   1.466  0.1428
## institution2          -0.03148    0.17857  -0.176  0.8601
## experience5-10y-<5y     0.30767    0.28040   1.097  0.2725
## experience>10y-5-10y   0.13731    0.29742   0.462  0.6443
## userpartly-no         -0.67513    0.34415  -1.962  0.0498 *
## useryes-partly         0.28866    0.34439   0.838  0.4019
## ---
```

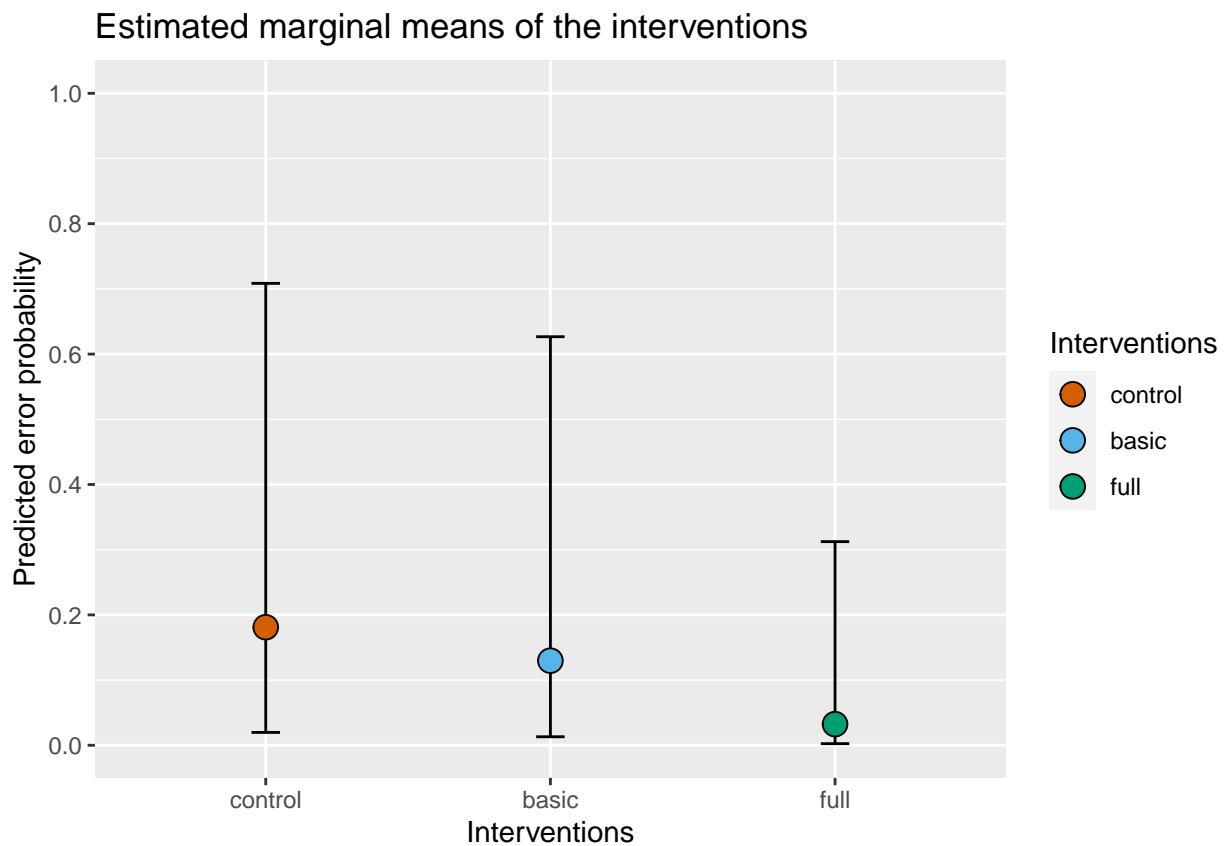


```

1  ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
2  ##
3  ## Correlation of Fixed Effects:
4  ##
5  ##      (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
6  ## intrvntnbs-  0.043
7  ## intrvntnfl-  0.277 -0.374
8  ## institutin1 -0.173 -0.002   -0.010
9  ## institutin2 -0.098 -0.006   -0.005   -0.345
10 ## expr5-10-<5  0.019  0.000   -0.010   -0.042 -0.314
11 ## exp>10-5-10  0.061 -0.004    0.005    0.146  0.070 -0.431
12 ## userprtly-n  0.239  0.007    0.007   -0.312  0.178 -0.039 -0.037
13 ## usrysys-prtly -0.137 -0.009    0.002   -0.324  0.113  0.023  0.025 -0.529
14
15
16

```

Plot - Predicted probability of error



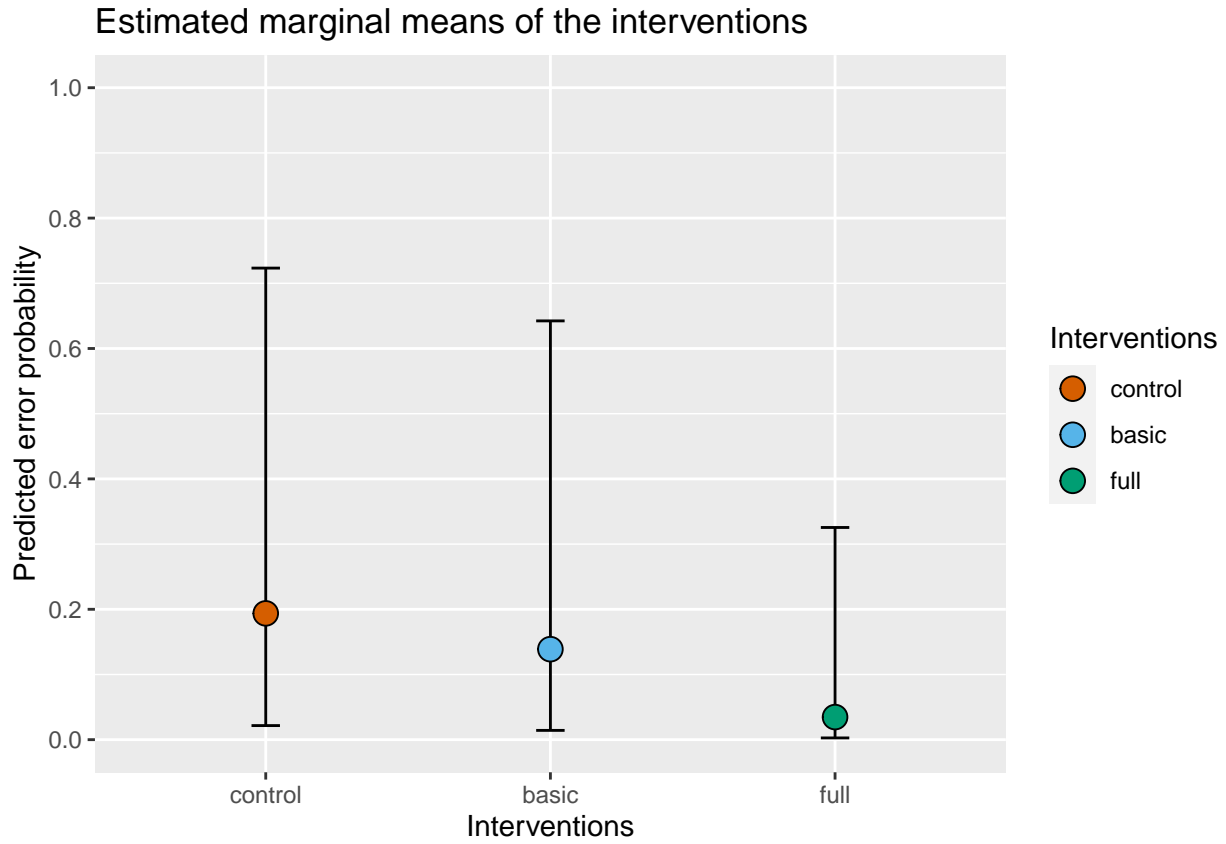
Errors (simple model)**Results**

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.02	0.0629
Intervention (full vs basic)	0.22	0.12	0.41	<0.001

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##           AIC      BIC   logLik deviance df.resid
##      706.8    731.0   -348.4   696.8     927
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -0.9847 -0.4297 -0.3089 -0.1722  5.7553
##
## Random effects:
##  Groups Name          Variance Std.Dev.
##  subject (Intercept) 0.2545    0.5044
##  item    (Intercept) 0.3500    0.5916
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1927    0.2047 -10.710 < 2e-16 ***
## interventionbasic-control -0.3994    0.2148  -1.860  0.0629 .
## interventionfull-basic  -1.5014    0.3169  -4.738 2.16e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.044
## intrvntnfl-  0.282 -0.375
```

Plot - Predicted probability of error



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Time (full model)

Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.95	-27.14	-12.06	<0.001
Intervention (full vs basic)	-30.99	-38.42	-22.67	<0.001
Institution (Children's hospital)	-18.44	-26.38	-9.64	<0.001
Institution (Hospital)	2.75	-5.83	12.12	0.5453
Experience (5-10y vs <5y)	1.85	-11.10	16.69	0.7926
Experience (>10y vs 5-10y)	-2.43	-16.02	13.36	0.7493
User (partly vs no)	-0.88	-15.39	16.12	0.9133
User (yes vs partly)	-5.87	-19.92	10.63	0.4666

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula:
## log_time ~ intervention + institution + experience + user + (intervention |
##   subject) + (intervention | item)
##   Data: data_exploratory
##
## REML criterion at convergence: 653.6
##
## Scaled residuals:
##   Min      1Q  Median      3Q      Max
## -4.1903 -0.5998 -0.0537  0.5331  3.2470
##
## Random effects:
##   Groups   Name                Variance Std.Dev. Corr
##   subject  (Intercept)          0.03751  0.1937
##           interventionbasic-control 0.03513  0.1874  0.10
##           interventionfull-basic    0.06151  0.2480  0.02 -0.47
##   item     (Intercept)          0.04184  0.2045
##           interventionbasic-control 0.01928  0.1388  0.01
##           interventionfull-basic    0.02960  0.1721 -0.76 -0.48
## Residual                    0.08292  0.2880
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)    4.842339   0.057639 30.008155  84.011 < 2e-16 ***
## interventionbasic-control -0.222575   0.048001 28.046824  -4.637 7.46e-05 ***
## interventionfull-basic   -0.370936   0.058103 30.941660  -6.384 4.17e-07 ***
## institution1    -0.203848   0.052280 44.997416  -3.899 0.000319 ***
## institution2     0.027128   0.044511 44.920751   0.609 0.545288
## experience5-10y-<5y    0.018346   0.069372 44.871124   0.264 0.792633
## experience>10y-5-10y -0.024608   0.076541 44.953549  -0.321 0.749324
## userpartly-no    -0.008842   0.080746 44.900724  -0.110 0.913292
## useryes-partly   -0.060522   0.082432 45.008740  -0.734 0.466626
## ---
```

Time (full model)

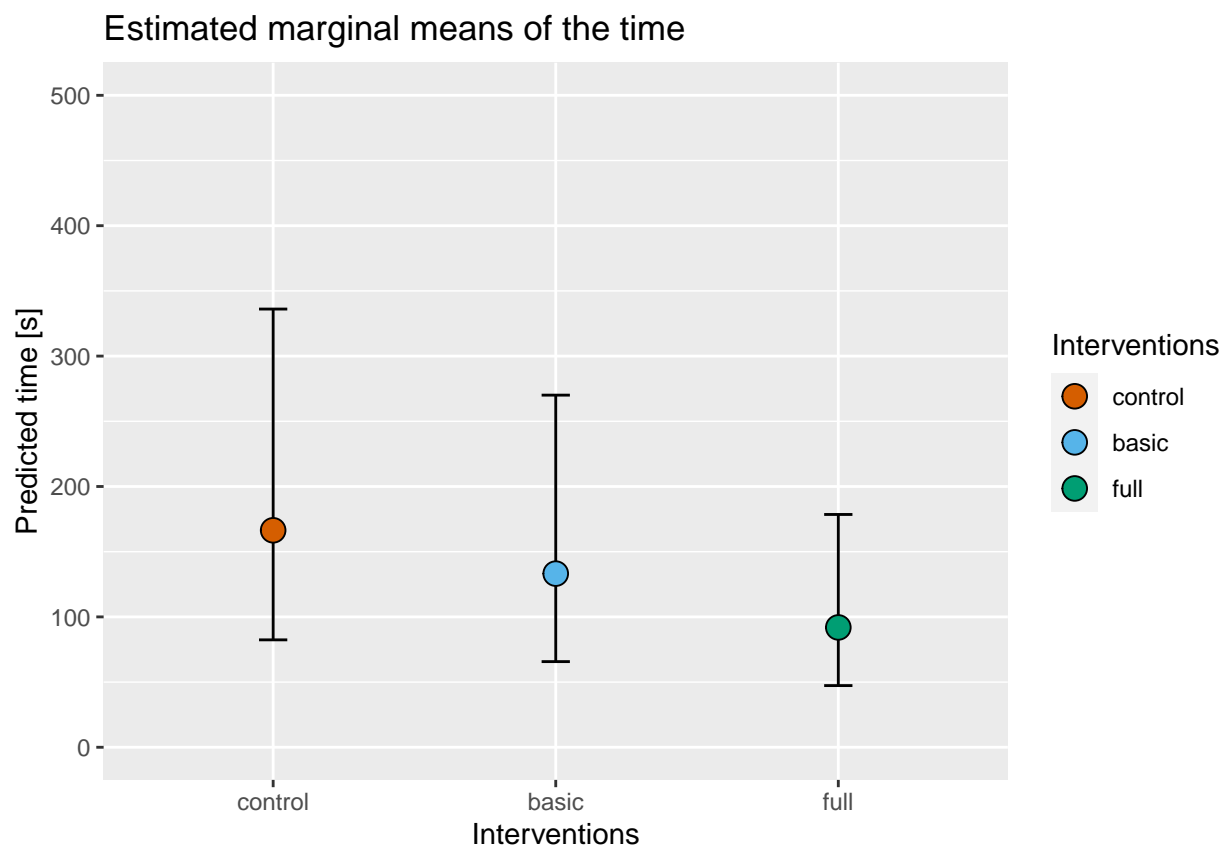
EXPLORATORY ANALYSIS

```

1
2
3  ## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
4  ##
5  ## Correlation of Fixed Effects:
6  ##          (Intr) intrvntnb- intrvntnf- instt1 instt2 e5-10- e>10-5 usrpr-
7  ## intrvntnbs-  0.030
8  ## intrvntnfl- -0.439 -0.476
9  ## institutin1 -0.083  0.001   -0.001
10 ## institutin2 -0.075  0.000    0.000   -0.412
11 ## expr5-10-<5  0.045 -0.001    0.000   -0.028 -0.312
12 ## exp>10-5-10  0.073  0.000    0.000    0.158  0.035 -0.442
13 ## userprtly-n  0.134  0.001    0.001   -0.292  0.200 -0.043 -0.046
14 ## usry-sprtly -0.086 -0.002    0.001   -0.374  0.134  0.001  0.007 -0.467
15
16

```

Plot - Predicted response time



Time (simple model)

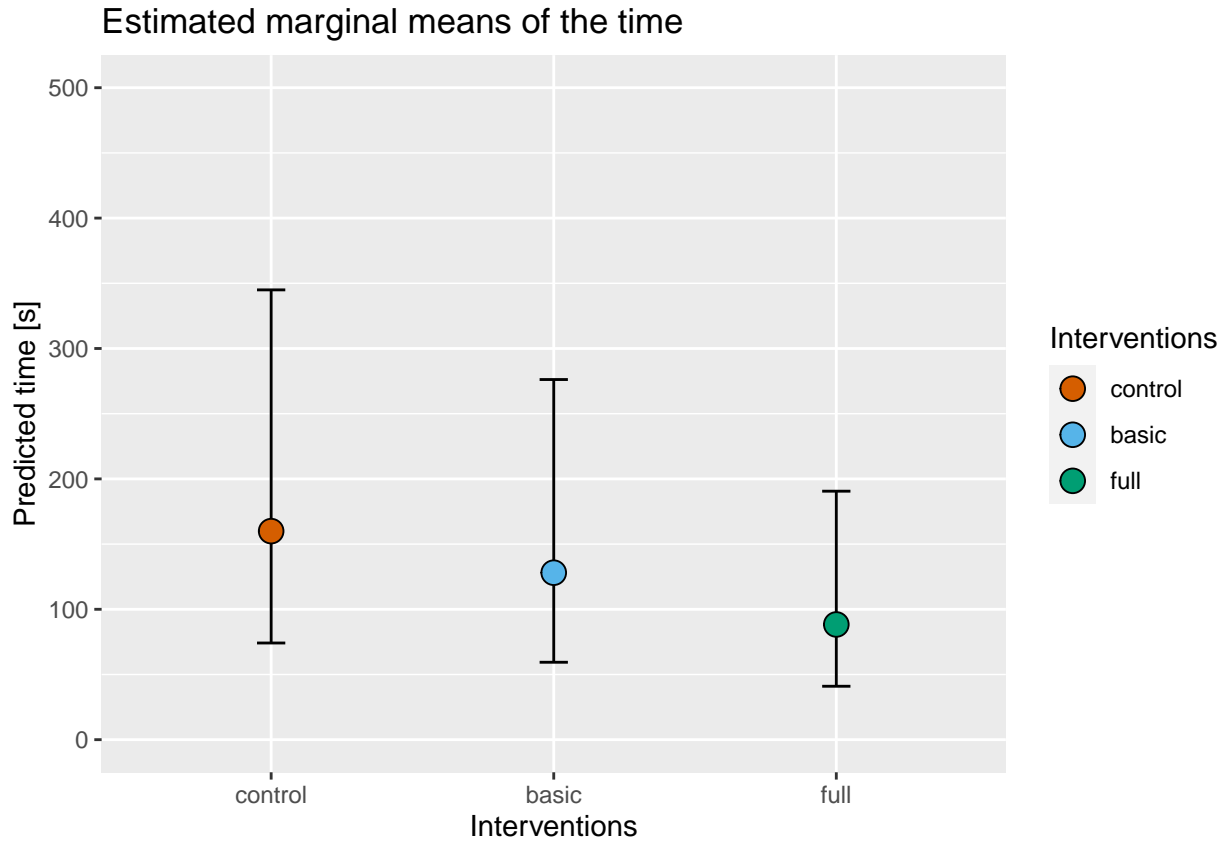
Results

Variable	Deviation (%)	CI (low)	CI (high)	p value
Intervention (basic vs control)	-19.93	-24.01	-15.62	<0.001
Intervention (full vs basic)	-31.01	-34.51	-27.32	<0.001

R summary output

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: log_time ~ intervention + (1 | subject) + (1 | item)
## Data: data_exploratory
##
## REML criterion at convergence: 762.6
##
## Scaled residuals:
##   Min       1Q   Median       3Q      Max
## -3.7745 -0.6461 -0.0532  0.6139  3.7661
##
## Random effects:
##   Groups   Name                Variance Std.Dev.
##   subject  (Intercept)          0.06287  0.2507
##   item     (Intercept)          0.04405  0.2099
##   Residual                               0.10814  0.3288
## Number of obs: 930, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error    df t value Pr(>|t|)
## (Intercept)      4.80288    0.06142 33.80208  78.194 < 2e-16 ***
## interventionbasic-control -0.22223    0.02671 861.13236  -8.319 3.45e-16 ***
## interventionfull-basic  -0.37118    0.02660 860.23224 -13.953 < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb-
## intrvntnbs-  0.000
## intrvntnfl-  0.001 -0.495
```

Plot - Predicted response time



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Sensitivity analysis

Results

Variable	OR	CI (low)	CI (high)	p value
Intervention (basic vs control)	0.67	0.44	1.03	0.0664
Intervention (full vs basic)	0.22	0.12	0.42	<0.001
Order (block 2 vs block 1)	1.14	0.71	1.83	0.5822
Order (block 3 vs block 1)	0.80	0.49	1.32	0.3783

R summary output

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: error ~ intervention + block_order + (1 | subject) + (1 | item)
## Data: data_exploratory
## Control: glmerControl(optimizer = "bobyqa")
##
##      AIC      BIC    logLik deviance df.resid
##    708.8    742.7   -347.4    694.8     925
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0778 -0.4245 -0.3108 -0.1725  6.5485
##
## Random effects:
##  Groups Name      Variance Std.Dev.
##  subject (Intercept) 0.2403   0.4902
##  item    (Intercept) 0.3724   0.6102
## Number of obs: 932, groups:  subject, 52; item, 18
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)      -2.1675     0.2493  -8.693 < 2e-16 ***
## interventionbasic-control -0.3950     0.2152  -1.835  0.0664 .
## interventionfull-basic  -1.4935     0.3173  -4.707 2.51e-06 ***
## block_order2         0.1327     0.2412   0.550  0.5822
## block_order3        -0.2238     0.2541  -0.881  0.3783
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) intrvntnb- intrvntnf- blk_2
## intrvntnbs-   0.049
## intrvntnfl-   0.212 -0.376
## block_ordr2  -0.497 -0.022   0.031
## block_ordr3  -0.466 -0.024   0.023   0.494
```

Contrasts

Contrast matrices for categorical variables

Intervention (exploratory)

```
##          basic-control full-basic
## control  -0.6666667 -0.3333333
## basic    0.3333333 -0.3333333
## full     0.3333333  0.6666667
```

User

```
##          partly-no yes-partly
## no      -0.6666667 -0.3333333
## partly  0.3333333 -0.3333333
## yes     0.3333333  0.6666667
```

Experience

```
##          5-10y-<5y >10y-5-10y
## <5y      -0.6666667 -0.3333333
## 5-10y    0.3333333 -0.3333333
## >10y     0.3333333  0.6666667
```

Institution

```
##          [,1] [,2]
## Children's hospital  1  0
## Hospital             0  1
## Community            -1 -1
```