

Swiss National Science Foundation project funding application

Title of the project:

Reducing Prehospital Pediatric Medication Errors and Time to Drug Preparation and Delivery by EMS in Switzerland: a Multicenter, Prospective, Randomized Controlled Trial.

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- a. Sponsor (within the meaning of the Ordinance on Clinical Trials in Human Research of 20 September 2013, article 2)

None.

1. Summary of the research plan

Background: Children represent a vulnerable population with specific medical needs compared to adults. Preparing intravenous (IV) drugs for critically ill children when required during resuscitation is particularly challenging. The urgent need to quickly and accurately prepare such drugs in a stressful environment places children at a particularly higher risk for medication errors than adults and is time-consuming. These errors are largely related to the need for individual specific weight-based drug doses calculation and preparation that vary greatly from birth to adolescence. In-hospital medication errors have been reported in 41% of pediatric resuscitation, the most common error being incorrect medication dosage in 65% of cases. However, a big challenge remains. The rate of errors may indeed be worse in the high-risk prehospital setting where care has to be delivered quickly by emergency medical services (EMS), in challenging field environments and where resources and providers are limited. Moreover, as paramedics have little exposure to critically ill children, they have limited opportunities to administer resuscitation drugs at pediatric doses. This may result in potentially life-threatening outcomes. Despite efforts to solve this problematic, prehospital preparation and delivery of emergency drugs remain a worldwide-unanswered health challenge with major impact on risk of medication errors, resuscitation duration, and healthcare economy.

To address this problem, we developed a tablet application, called Pediatric Accurate Medication In Emergency Situations (PedAMINES). This app is a supportive tool designed to drive caregivers step-by-step and in real-time from preparation to delivery of a wide range of drugs, especially those required during resuscitation. We conducted a prior multicentric randomized controlled crossover trial granted by the *Swiss National Science Foundation* in 6 pediatric emergency departments in Switzerland during a simulation-based pediatric cardiac arrest scenario. Medication errors were reduced from 75.9% to 10.2% by using respectively conventional preparation methods or PedAMINES ($P < .0001$). While using PedAMINES time to drug preparation (TDP) and delivery (TDD) were reduced by 147.5 (48%) and 170.5 (39%) seconds respectively (both $P < .0001$). However, the app was not assessed in prehospital settings.

Objectives: we aim to determine whether the use of PedAMINES improves the management of acute pediatric prehospital life-threatening conditions in Switzerland by quickly delivering expertise in IV drugs administration and by avoiding medication errors. We hypothesize that PedAMINES will reduce medication errors, TDP and TDD independently of the existing conventional preparation methods used or EMS' skills.

Method: a multicenter, prospective, unblinded, randomized controlled trial to compare the efficacy of PedAMINES vs conventional methods in the preparation of IV emergency medications during a video-recorded simulation-based pediatric cardiac arrest scenario. **Participants:** 120 paramedics in several EMS all over Switzerland. **Randomization:** stratified on EMS and centralized with a 1:1 allocation ratio. The study is formatted according to the CONSORT-EHEALTH and the Reporting Guidelines for Health Care Simulation Research statements.

Intervention: each paramedic will be asked to prepare a standardized series of 4 IV emergency medications, using either PedAMINES (intervention group) or conventional methods (control group). Two questionnaires will be given before and after the scenario to collect paramedics' demographics data and satisfaction. Stress level will be assessed by questionnaire and heart rate will be recorded as a stress marker with a fitness watch.

Outcomes: the primary outcome is to measure the absolute number and the rate of medication dosage errors committed during drugs preparation sequences until injection in each allocation group. The secondary outcomes are the delays in seconds to TDP and TDD in each drug completion sequence, as well as other medication errors, perceived and measured stress. Acceptability and usability testing of the app will be assessed using a 52-item questionnaire based on the unified theory of acceptance and use of technology (UTAUT) model.

Perspectives: PedAMINES might help EMS with different competencies to prepare and deliver complicated drugs. This suggests a worthwhile benefit to its use in remote places where paramedics are little exposed to pediatric resuscitation but have to use resuscitative drugs before to transfer the patient to a tertiary care center. Being able to assess PedAMINES in the prehospital setting would be the next step to demonstrate its usefulness in multiple settings before to deploy the application all over Switzerland in real situations. It will also standardize and unify drugs prescription in Switzerland during the whole pre- and in-hospital resuscitation process. Finally, our project will also be beneficial to clinical research in Switzerland by offering a common base for further studies on prehospital medication errors.

2. Research plan

2.1 Current state of research in the field

Despite many advances in the medical field in recent years and in particular in emergency medicine, suboptimal quality of resuscitation is still common for both adult and pediatric patients¹. Currently, the median hospital survival rate from pediatric in-hospital cardiopulmonary arrest (IHCA) is 36%¹, whereas it is below 10% for out-of-hospital cardiopulmonary arrest (OHCA)^{2,3}. According to the American Heart Association, emergency medications such as epinephrine, adenosine or amiodarone have to be considered in children undergoing pediatric advanced life support^{4,5}. Many situations do also require use of drugs or substrates for acute pediatric problems that require pharmacologic intervention to restore vital functions and prevent patients from deteriorating (ex: anticonvulsive drugs, dextrose, etc). However, quickly, accurately, and safely preparing intravenous (IV) drugs in a stressful environment is particularly challenging, error-prone and time-consuming⁶⁻⁹ when required during emergent pediatric situations.

Medication errors: Medication errors are common in pediatric patients. These errors are largely due to the need for individual specific weight-based drug doses calculation and preparation that vary significantly from birth to adolescence^{7,10-14}, as well as a lower dosing-error tolerance¹⁵. Whereas emergency medications given to adults being resuscitated are typically in prefilled ready-to-inject syringes containing a single dose adapted for most patients, majority of drugs given to pediatric patients are provided in vials not adapted for this population, leading to the need to manipulate drugs, to adapt volumes, concentrations and doses. This often requires micro-calculation for a majority of drug concentrations that are initially appropriate for adults rather than children. This places children at higher risk than adults for errors^{7,10,11} and may result in life-threatening outcomes. The rate of medication errors also increases in emergency care requiring various drugs administration where each of which may have its own concentration, dose, and volume⁷.

In the hospital setting, critically ill or injured patients are typically admitted in pediatric emergency departments (PEDs). A recent study showed that one in every 32 prescriptions in a PED contained a tenfold error on the recommended dose⁷. Medication errors have been reported in up to 41% of pediatric cardiopulmonary resuscitations (CPR) in PEDs, the most common being incorrect medication dosage, found in up to 65% of cases¹⁶. Kozer et al showed an error rate of 17% at the prescription level, with up to 10 times the recommended pediatric dose in more than 3% of the cases¹⁷. In the same study, 16% of the analyzed syringes showed a 20% dose deviation from the prescribed dose and up to 7% showed a deviation of more than 50%.

Furthermore, the rate of medication errors may be made worse depending on the situation in which the drugs are being given. This is especially true in the high-risk prehospital setting where care has to be delivered quickly and where resources are limited. A single paramedic is often in charge of determining the patient's weight, choosing the most suitable drug, calculating the drug dose and appropriate volume to inject, and administering it to the patient. Several specific aspects of pediatric care in the prehospital setting may also increase the risk of medication errors¹⁸. The time pressure to prepare the drugs on-site adds to the complexity of the process. Compared to children who arrive at the emergency department by other means, children transported by emergency medical services (EMS) are indeed more likely to require immediate care¹⁸. Disruptive emotional anxiety and exogenous conditions encountered during prehospital pediatric resuscitation, such as challenging field environments and parental stress, may also increase cognitive load^{19,20}. Moreover cognitive load has been shown to be higher and error-prone when the task is less familiar, as typically seen during CPR²¹, and uncommon like in children^{19,22}. As is the case in the U.S.A.²³, pediatric patients are only seen in about 7% of EMS calls in Switzerland²⁴. Paramedics have therefore little exposure to critically ill children and experience to administer emergency medications at pediatric doses²⁵. For instance, it was shown that delivery of epinephrine and dextrose to children less than 17 years old by EMS in 26 U.S.A. states accounted for only 3,6% and 0,8% of the total adult drug administrations respectively. Consequently, EMS have minimal opportunities to gain experience and maintain competence in this skill^{26,27}. This sum up to the fact that almost 60% of paramedics report their initial education course as deficient pediatric-specific training²⁶.

Therefore, knowing that medication errors still occur in PEDs despite favourable well equipped and staffed environments with numerous available safeguards, it is not surprising that the aforementioned factors expose EMS to greater opportunities for medication error rates and patients harm in the prehospital setting. It has been shown in a large study that prehospital medication dosing errors affect approximately 56,000 U.S. children treated by EMS each year²⁶. Authors showed that drugs were administered outside of the proper dose range in up to 39,8% of more than 5500 children. Among other drugs, epinephrine had the highest rates of incorrect doses with 60,9% of preparations containing an error, and a mean error overdose of 808%. Among EMS, 55% used a Broselow-Luten length-based tape (BLT), while 36% asked the parent or guardian to estimate weights, and 2.3% relied on a smart phone app. These results were in agreement with those of other studies where providing EMS with ready access to a BLT were shown to be insufficient to prevent a high rate of epinephrine errors in the prehospital setting with dosing errors exceeding 60 to 70%^{25,28}. In another study identifying causes of errors by EMS during a simulated prehospital pediatric emergency,

the error rate for diazepam and midazolam dosing was 47% and 60% respectively²⁹. Underlying causes of errors included incorrect estimation of weight, incorrect use of the BLT, incorrect recall of doses, difficulty with calculations under stress, mg/kg to mg to mL conversion errors, inaccurate measurement of volumes, and failure to cross check doses between providers²⁹. These results were somehow similar to others reporting that paramedics commit dosing errors 49–63% of the time with miscalculation as a primary cause¹¹. Even after intervention to instruct EMS in the use of the BLT and precalculated drug dosing charts, medication dosing errors remain significant²⁵. This highlights the fact that the sole expertise of paramedics helped by conventional conversion methods is not sufficient to ensure fast and reliable conversion and preparation of IV emergency medications. At this stage, even small errors either in weight estimation or drug calculation may have a large detrimental impact on the amount of drug delivered³⁰⁻³². This can be deleterious to critically ill and unstable patients and even prove fatal⁷. Some authors have therefore advocated replacing as much as possible tasks requiring cognitive load during CPR by automated actions in order to optimize patient care and diminish medication errors^{21,33}. Moreira et al. have shown that the use of color-coded prefilled medication syringes in a PED reduced by 17% the risk of medication errors during simulated pediatric resuscitations³³. However, if prefilled syringes appear to be applicable for drugs that can be packaged as ready-to-use medications in PEDs, it is less evident for drugs used in the prehospital setting³⁴. The number of drugs available, their chemical stability over time³⁵⁻³⁸, the infrequent EMS calls for children, and the wide range of drug doses used in this population would render this solution nonviable and economically unjustified. Thus, to date, drugs administered out-of-hospital continue to need upstream preparation and medication errors remain a worldwide health challenge with major economic impact.

Every minute counts: In resuscitations, time is also a decisive success criterion. It is well established that cardiopulmonary resuscitation (CPR) duration is inversely correlated to survival. During the first 15 minutes of in-hospital cardiac arrest (INHCA) pediatric resuscitation, survival and favorable neurological outcome decrease linearly by 2.1% and 1.2% per minute, respectively³⁹. Thus, the survival rate for CPR less than 15 minutes is estimated at 41 %, while this rate drops to 12% after 35 minutes³⁹. Similarly, among pediatric patients with out-of-hospital cardiac arrest (OHCA) with non-shockable initial rhythms, each minute delay to epinephrine delivery is associated with 9% decrease in the odds of survival^{40,41}. Regrettably, in the prehospital setting, the majority of patients receive epinephrine more than 10 minutes after EMS arrival^{40,41}. The chain of survival therefore critically relies on early prehospital initiation and efficient resuscitation by EMS⁴², onsite administration of certain drugs without delay^{40,41,43,44} before a rapid transfer to PED and advanced care.

2.2 Current state of our own research

PedAMINES: Following a user-centered and evidence-based approach⁴⁵, our group composed of PED physicians and nurses, as well as software developers and ergonomists has developed a tablet app called Pediatric Accurate Medication in Emergency Situations (PedAMINES). This app is a supportive tool designed to drive caregivers step-by-step and in real-time from preparation to delivery of a wide range of drugs, especially those required during resuscitation. The app development was mainly guided by requirements built on our clinical experience, CPR observations and focus groups⁴⁶. In an in-hospital pilot randomized trial, we have shown that medication errors were reduced from 70% to 0% ($P<.001$) by using PedAMINES when compared with conventional methods. Time to drug preparation (TDP) and delivery (TDD) were decreased by 180 and 177.3 seconds respectively ($P=.002$)⁴⁷. Results were by far better than those, already consequent, obtained with the on-site presence of clinical pharmacist during pediatric CPRs associated with a 25% decrease in medication errors¹⁶.

Granted by the *Swiss National Science Foundation* (SNSF #**32003B_169348/1**), we next conducted in 2017 a multicentric opened randomized controlled crossover trial in 6 PEDs in Switzerland with the same simulation-based scenario with more than 120 nurses (forthcoming publication). Medication errors were reduced from 75.9% to 10.2% by using PedAMINES when compared with conventional methods ($P<.0001$), while using PedAMINES TDP and TDD were reduced by 141.8 (43.9%) and 161.9 (39.0%) seconds respectively (both $P<.0001$, Figure 1). Participants rated the overall perceived satisfaction using PedAMINES to be 9.4 (95% CI 9.3-9.6) on a 10-point Likert scale.

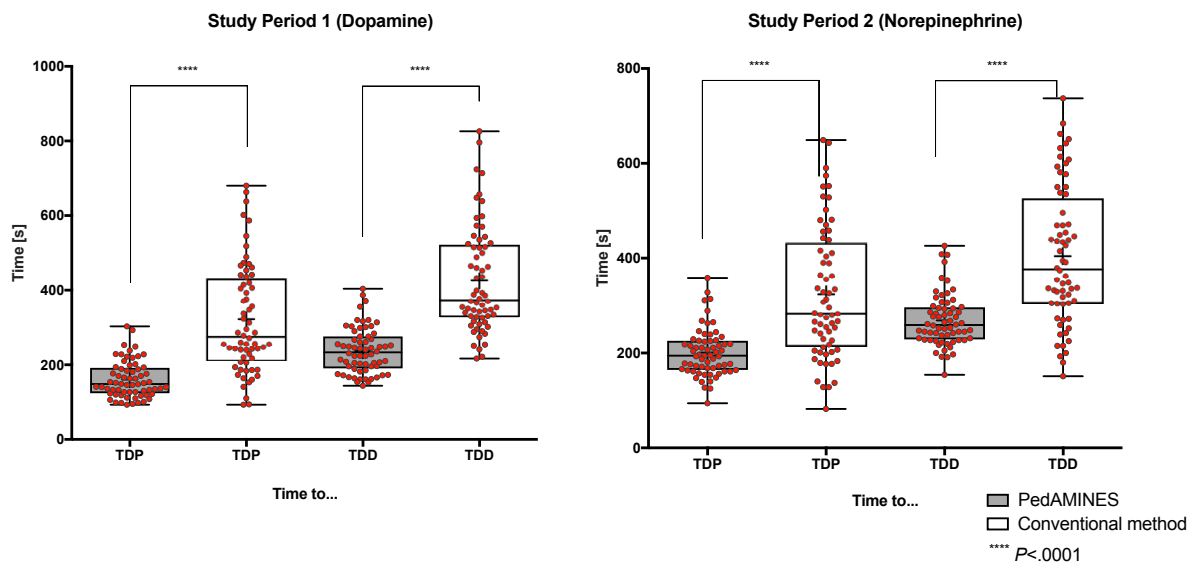


Fig 1. Boxplots of elapsed time to drug preparation (TDP) and to drug delivery (TDD) in intervention group (PedAMINES) and control group (conventional method) in both periods of the SNSF crossover study. Time is expressed in seconds. Solid horizontal lines denote median and interquartile ranges; the whiskers go down to the smallest value and up to the largest; + denotes mean. Red open circles denote each individual value. Time is expressed in seconds. P-values are the result of Mann-Whitney test. **** $P<.0001$.

PedAMINES is much more than just a calculator. The app lists all the available resuscitation drugs, either for direct IV or continuous infusion, with doses automatically adapted to the weight or age of the patient entered when starting the app. The list can be expanded and customized according to users' need and to local drugs habits internationally. Drugs (concentration, volume, etc.) are fully editable to adjust for each center internationally. Safety of the app (doses, calculations, etc.) is guaranteed both by the calculation algorithm created and checked by the developers' team and by the data edited by each user. By a simple touch, any of the listed drugs can be selected and the exact amount to prepare is clearly displayed making calculations useless (Figure 2). This is based on the app's ability to automatically calculate the optimal weight-based drug dose, independently of the user competency in this domain. Multiple drugs can be prepared and run in parallel. All actions performed are stored locally on the device in historic files to preserve information that can be retrieved at any time for debriefing or medicolegal purposes. Historic files can also be erased or safely exported and saved in electronic health records. PedAMINES is so simple to use and powerful that even inexperienced users may use it after a 5-minutes training session. This was particularly obvious in our SNSF granted study where distribution of individual delays was less spread with PedAMINES than with the conventional method (Figure 1). This suggests a worthwhile benefit to its use in the prehospital setting where paramedics are infrequently exposed to pediatric CPR but have to use resuscitative drugs before to transfer the patient to a tertiary care center.



Fig 2. PedAMINES application screenshot

Need for a trial: To our knowledge, PedAMINES is the first scientifically validated app to improve drug preparation during in-hospital pediatric CPR and able to sustain cognitively users during this process. However, a big challenge remains. To date, very few pediatric studies of medication errors and error prevention strategies have been performed in

prehospital settings, particularly in regard to the care of pediatric patients^{18,26}. This translates into suboptimal knowledge and delivery of pediatric prehospital care. It remains to be determined whether the use of PedAMINES will improve the management of prehospital life-threatening conditions in prehospital setting, where EMS are either little or not exposed to pediatric resuscitation. As research in this area is scarce, results generated from this study will be of great importance. They might be sufficient to change and improve the pediatric prehospital emergency care practice and increase survival rate. Importantly, PedAMINES might become an efficient tool to standardize and unify CPR's drugs prescription during the whole pre- and in-hospital resuscitation process in Switzerland. A large multi-center randomized trial is therefore needed to assess this assumption in the prehospital setting.

2.3 Detailed research plan

2.3.1. Choice of comparators

In Switzerland, EMS providers have autonomy in emergency situations and a delegated authority to prepare emergency medications. They should therefore be regarded as medication prescribers for the purpose of studying medication errors in the prehospital setting. The current, conventional method used to prepare such drugs relies on the use of the BLT, protocols or precalculated drug dosing charts.

In our pilot and SNSF studies PedAMINES has been validated as an efficient tool to reduce medication errors and delays in CPR. Its selection as comparator is therefore justified.

2.3.2. Objectives and hypothesis

We aim to determine whether the prehospital use of PedAMINES by EMS in Switzerland reduces medication errors, as well as TDP and TDD.

Research hypothesis: Herein, we hypothesize that PedAMINES reduces medication errors and TDP and TDD independently of existing conventional preparation methods (i.e. precalculated drug dosing charts) or EMS' skills.

Primary objective: To determine whether prehospital use of PedAMINES during pediatric resuscitation reduces medication preparation errors compared with conventional methods.

Secondary objective: To determine whether prehospital use of PedAMINES during pediatric resuscitation reduces dosing deviations and other types of errors (see below) compared with conventional methods. To determine if PedAMINES leads to a shorter time in direct IV drugs preparation (TDP) and delivery (TDD).

2.3.3. Study design

The study is a prospective, multicenter, randomized controlled trial with 2 parallel groups comparing PedAMINES^{46,47} with conventional precalculated drug dosing charts used by EMS in the preparation of direct IV drugs during a standardized simulation-based pediatric cardiac arrest scenario. The drug dosing charts is presented as a spreadsheet, enabling the preparation of the commonly ordered concentrations of emergency medications at varying dose ranges based on the patient's weight. To calculate the composition of the drug to inject, one first selects the desired drug dosage to be delivered in mg/kg. The next step is to calculate the milliliters of drug based on the weight of the patient to be diluted with compatible fluids (sodium chloride 0.9%, etc) in a syringe. For the purpose of the study, we will not select drugs that can be directly drawn from the vial without calculation and dilution.

The multicentric setting of the study will involve 15 Swiss EMS (Cantons of Geneva, Vaud, Neuchâtel, Fribourg, Jura, Zurich, Bern, Basel, Lucern, Ticino). To ensure optimal quality of reporting, the trial is formatted according to the Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth (CONSORT-EHEALTH)⁴⁸ and the Reporting Guidelines for Health Care Simulation Research⁴⁹

2.3.4. Inclusion and exclusion criteria

Registered paramedics are eligible for inclusion in this study. Participants must know how to prepare IV drug injections, and be willing and able to grant written informed consent. Written informed consent will be obtained from all the participants before their voluntary involvement.

2.3.5. Intervention

2.3.5.1. Interventions

The scenario in this study is a short, approximately 20-minute, standardized highly realistic pediatric resuscitation simulation on a wireless high-fidelity manikin (Laerdal New SimBaby). The SimBaby represents a realistic 1-year-old boy. The choice of selecting this manikin is directed by our willingness to simulate resuscitation in a young child requiring pediatric drug dosage, and also to take advantage of its wireless properties allowing its use in pre-hospital conditions. This simulator provides all functionalities that are relevant to assess the research questions, including chest compression, ventilation, vascular access, seizure, as well as realistic and interactive vital signs. To date, high-fidelity simulation has become essential to study resuscitations skills and technologies that cannot be practiced during both prehospital and in-hospital

resuscitations because interindividual diversity among patients and their diseases make CPR studies hard to standardize in critical situations⁵⁰. When skills are assessed with simulations, errors are made more visible than during actual pediatric prehospital resuscitations²⁹. Moreover, by standardizing the scenario and environment, we will avoid effect modifiers by preventing the influence of undesired variables on the outcomes. To date, none of the results obtained from simulation-based CPR studies disagreed with those obtained from studies in real life.

Consistent with standard emergency medicine practice, we will create resuscitation teams. Two members from the study team, remaining the same along the whole study period, will assist the study participant. A Pediatric Advanced Life Support (PALS) instructor-certified emergency pediatrician will lead the resuscitation, and a nurse playing the role of a second paramedic will assist with resuscitation by performing chest compressions and bag-valve mask ventilation according to the pediatrician instructions, but not drug dose calculation or preparation. Participants will be informed before the scenario starts that these 2 people are study team members. Both study team members will guide each participant through a series of predefined key steps, blinded to the participant, following a standardized resuscitation scenario (see below). The physician will order the medications and allow progression through the scenario only once predefined milestones have been reached, regardless of the occurrence of errors or time to achieve them. The study-specific training and standardization of both study team members is ensured through their involvement in the pilot study⁴⁷ and previous SNSF study and by following the predefined scenario. A certified technician will operate the simulator.

On the day of participation, paramedics will complete a survey collecting data regarding their demographics, care training, and simulation and computer experience. After random allocation, each participating paramedic will receive a standardized 5-minute training session on how to use the PedAMINES app. Paramedics will remain unaware of drugs that will be used and specific endpoints of the study during this training session. The simulation manikin characteristics are then presented. The paramedics will then be asked to perform the pediatric resuscitation scenario. This scenario is standardized to follow the same chronological progression and range of difficulty to ensure each participant is exposed to exactly the same case, with similar challenges in decision making and treatment preparation provided on the same manikin. The uniform delivery of the scenario all along the study will minimize confounders. Study team members will only adapt to progression speed of participants through the scenario by maintaining a stressful resuscitation atmosphere. The scenario will be videorecorded and conducted in a simulated children room in each area in order to increase realism. High levels of realism are known to immerse participants in the simulated experience and prevent confounding

variables that might potentially affect the way individuals perform⁵⁰. The simulated room will be exclusively devoted to the simulation to prevent unexpected interruption or external stimuli. Portable monitoring alarms will be activated to increase realism and stress. All usual EMS resuscitation equipment will be at the disposal of the paramedic. In both allocation groups, the decision to use or not use any equipment will remain personal as in real life. Neither pilot testing nor repetitions will be permitted. There will be neither interventions nor educational adjuncts prior to or after the study period. Once the experiment completed, the paramedic will be required to recall and describe precisely how he prepared the drugs in order to verify that the drug names and original doses prescribed by the physician were correctly understood to assess the presence of comprehension bias.

Resuscitation scenario: the untimed portion of the simulation starts by turning on the video cameras and the fitness watch. The paramedic and both investigators (the confederate paramedic and the physician) wait outside the room where they are supposedly dispatched. The team will be invited to enter the room by the father (simulated by the technician operating the manikin). A clinical statement to recognize the life-threatening condition of the patient, including his weight and age, is then given by the father as follows: "Here is Junior, a 12-kg, 1 and a half year old boy who suddenly collapsed 15 minutes ago. Oral tricyclic antidepressant as well as antidiabetic pills from his grandmother were found in his mouth and on the ground of his room. He is unconscious, pale and does not breathe". At this moment, the physician asks the participant to take a central pulse. Because of the invariable absence of a pulse, the latter is asked to assist the physician to perform a 2-min full course massage and ventilation (15:2 ratio) maneuver to increase his own stress level (massage carried out by the participant). During this time, the physician asks the confederate paramedic to place a 4-derivation electrocardiogram on the manikin, an upper arm blood pressure monitor, a digital pulse oximeter and defibrillator's patches. Then the physician asks to change roles; the confederate paramedic has to carry out the massage while the participant has to get a peripheral vascular access on the manikin's right hand. At this time, an asystole rhythm is recognized and verbalized by the physician. On the basis of the American Heart Association pediatric cardiac arrest algorithm for asystole⁴, a bolus of epinephrine is ordered by the physician and the timed scenario begins. The participant must prepare and administer the drug with the help of PedAMINES (intervention group) or following the conventional method. ROSC ensues with generalized tonic-clonic seizures. The physician says: "The patient has now a return of spontaneous circulation with a pulse but with seizures. This patient needs an IV bolus of midazolam right now". The seizures stop 15 seconds after administration of the drug. At this time the physician asks the participant to perform a finger stick to obtain a blood sample. The glucometer reports a blood sugar of 0.8 mmol/L. The physician says: "the patient has a severe

hypoglycemia” and prompts the participant to prepare and inject an IV bolus of dextrose 10%. Return of a state of consciousness ensues with normal vital signs, but a wide QRS on EKG-monitoring. The physician says: “This child needs an IV bolus of sodium bicarbonate 1 mEq/kg”. As soon as this last medication is administered, the physician asks for transport and the scenario ends. The cameras and the watch are turned off 1 minute later. The measured deviation between the amount of drug delivered and the actual prescribed dose will be measured by the amount of drug in the syringe. As everything is video-recorded, we will be able to verify and measure the exact amount of drug and concentration in the syringe after the scenario. During the whole scenario, the physician, the confederate paramedic and the operator will maintain a stressful resuscitation atmosphere (monitoring alarms are on, the primary assessment (ABCDE) is often repeated, vital signs are frequently reported aloud and the father repeatedly verbalizes his dismay).

2.3.5.2. Criteria for discontinuing or modifying interventions

The time needed to complete the full scenario was set to only a 20 minutes period for each participant and will be booked weeks ago to ensure availability of the participants without repercussion on their normal duty. All participants will receive full permission from their hierarchy to participate to the study. Using simulation-based CPR scenario makes our study highly feasible without risks for patients or participants.

2.3.5.3. Adherence

The study will take place during a 1-week period in each EMS and will occupy each paramedic for a single 60-minute period. Thanks to our experience gathered in previous studies, we anticipate a very low rate of drop-outs or loss of follow-up. To ensure the presence of participants on the day of participation, shift-working paramedics will be randomly recruited 1 month before the start of the study by a blinded noninvestigator. They will be informed of the upcoming simulation study but not of its purpose and outcomes. Each paramedic will be rewarded individually by an amount of 50.- CHF for its participation to the study. Adherence of the collaborating EMS to our study will be reinforced by their citation in further publications and by a privileged access to the PedAMINES app.

2.3.5.4. Concomitant care

The paramedics will be allowed to use their current, conventional method of preparing direct IV drugs, even if it differs between EMS. This will avoid introducing evaluation bias on the baseline ability of paramedic to prepare drugs “as usual” if allocated in the group without PedAMINES. This will also test the absolute capacity of the app to reduce medication errors and drugs delays, indifferently of the prior traditional method used.

However, participants will not be allowed to use any other drug support device and the scenario will remain secret until it starts to avoid upstream drugs preparation's refresh.

2.3.6. Outcomes

Primary outcome measures: The primary outcome will be to measure, in each allocation group, the number of medication dosing errors committed during each drug preparation sequence until injection. According to Marcin et al. and Moreira et al, we defined a emergency medication dose administration error as more than 10% deviation from the correct weight dose^{9,12}.

Secondary outcome measures: The secondary outcomes will be to measure, in each allocation group, the followings variables:

A) *Errors that might be encountered during drug preparation*, such as: 1) the amount of drug taken in mL and deviation from the one prescribed on the drug dosing charts or the app, 2) the amount in mL of saline solution taken to dilute the drug, and deviation from the one prescribed, 3) final drug concentration in mg/ml obtained and deviation from the one prescribed, 4) correct or wrong drug chosen by the paramedics compared to the one prescribed on the drug dosing charts or the app (the drugs chosen will be recorded for every participant in order to find any systematic or repetitive error), 5) correct or wrong air purge out of the syringe before injection, 6) correct or wrong labeling of the filled syringe, 7) detection or not of error(s) by the paramedics, 8) stage of error(s) detection: before or after injection, and 9) aseptic errors. These measures of medication errors were selected as they were considered to be the most common sources of medication errors as evidenced in the pediatric medication error literature and meta-analysis^{17,51,52}.

B) *The time points of the drug preparation, in each allocation group*, such as: 1) time in seconds between the end of the drug prescription by the physician and the syringe filled with the drug (TDP), 2) TDP plus time in seconds between TDP and injection (TDD). TDP and TDD are relevant temporal values described in the resuscitation literature^{39,53}.

C) *Questionnaires*: at the end of the scenario, a 6-item questionnaire using a 10-point Likert scale (scored from one to ten to avoid neutral answers) will be provided to the participants. The questionnaire measures (1) the overall stress perceived, (2) the stress perceived during each drug preparation sequence with PedAMINES and with the conventional method(s), and (3) the satisfaction about the preparation method used during the resuscitation scenario. Acceptability and usability testing of the app will be assessed using a 52-item questionnaire based on the unified theory of acceptance and use of technology (UTAUT) model⁵⁴. UTAUT provides a useful tool to assess the likelihood of success for new technology introductions and helps to understand the drivers of its acceptance.

D) *Heart rate (HR) as a stress marker*: a baseline HR before the beginning of the scenario as well as continuous HR monitoring of each participant reflecting his or her stress level will be recorded during the scenario. Mean delta HR values (difference between HR peak values and baseline HR) will be obtained during some small segments of scenario and correlated to the scenario phases and the preparation methods used.

2.3.7. Patients Timeline

On-site staff in every collaborating EMS will organize participation of paramedics to the study. No information about the ongoing study will be given to the paramedics at this stage. The best study period will be matched with study coordinators. The paramedics will be spread throughout 1 week in order to link up the several scenarios. On scheduled weeks, the study coordinators will visit the collaborating EMS, provide trial information to participants before they begin the scenario, and assessment of eligibility will be verified. Participants will then sign the informed consent. They will be asked to complete an anonymised demographic questionnaire and confirm their willingness to participate. If it's the case, they will pursue with a 5-minute learning session to the use of PedAMINES given by the investigators. Then, each participant will be randomly allocated to study arms. Immediately after the randomization, the paramedic will start the scenario. 1) the overall stress perceived during the scenario and during each drug preparation, and 2) the satisfaction about the preparation method used. The total study period to enroll all paramedics in the various EMS will take 12 months.

Table 1. PedAMINES timeline protocol for forms and procedures

	Study Period				
	Pre-enrollment	Enrollment / consent	Pre-study baseline / allocation	20-minute scenario	Closeout
Time point	$-t_2$	$-t_1$	0	t_1	t_x
ENROLMENT:					
Invitation to participate	X				
Eligibility screen		X			
Informed consent form		X			
Demographic questionnaire			X		
PedAMINES learning session			X		
Randomization			X		
INTERVENTION :					
Group A (with PedAMINES)				X	
Group B (with conventional method)				X	
Termination questionnaire					X
ASSESSMENTS :					
Medication errors				X	
Time at prescription				X	
Time to drug preparation (TDP) and delivery (TDD)				X	

2.3.8. Sample size

The primary objective of this study is to detect a difference in proportions of medication errors between groups (with PedAMINES vs without PedAMINES). The expected proportion of errors made without PedAMINES is 60%¹¹. We consider that a difference of 30% in the proportion of medication errors is sufficient to modify the practice. Therefore, the sample size was calculated to reach a statistical power of 90% in detecting an absolute difference of at least 30% in proportions of medication errors between intervention groups. With a two-sided risk alpha of 0.05, the needed sample size is 56 paramedics per arm of the study. To prevent a potential loss of power due to misspecification of assumptions, 60 paramedics will be recruited per randomized group (total sample size: 120 paramedics).

2.3.9. Recruitment

2.3.9.1. Recruitment strategies

We already have the study participation approval of the different EMS. Each collaborating EMS will organize a dedicated time slot for the study to be run and paramedics to be available at the defined period. In case of unavailability of a paramedic at the selected date, the collaborating EMS will handle to replace him. The investigators and collaborating EMS will be in close contact by phone/email to guarantee availability of the paramedics.

2.3.9.2. Feasibility of recruitment

The number of available paramedics will be guaranteed by the collaborating EMS knowing their absolute workforces and the paramedics working shifts. Given the calculated sample size, the number of paramedics is affordable.

2.3.10. Assignment of intervention

2.3.10.1. Allocation sequence

A single randomization of the participants (paramedics) will be done using an online computing web randomisation service⁵⁵ to generate the randomisation list. With this method, paramedics will be randomly assigned to either group A (using PedAMINES) or to group B (conventional preparation methods) with a single, constant 1:1 allocation ratio. One randomization list per EMS center will be produced (randomization stratified on center) and block of random size will be used to generate the randomization lists.

2.3.10.2. Concealment mechanism

Allocation concealment will be ensured with <http://www.sealedenvelope.com> and will not be released until the paramedics start the scenario.

2.3.10.3. Implementation

The allocation sequence will be generated by <http://www.sealedenvelope.com> and the randomization lists will remain with it for the whole duration of the study, ensuring that the investigators couldn't influence the lists. The paramedics will be enrolled and assigned to the allocation groups by the investigators of the study on the day of the simulation.

2.3.11. Blinding

2.3.11.1. Blinding

Blinding to the purpose of the study during recruitment will be maintained to minimize preparation bias. The paramedics will be unblinded after randomization. The study team members will be revealed just before the scenario starts, and video reviewing will be done without blinding by both video reviewers but independently and blindly from one another.

2.3.11.2. Emergency unblinding

At the time of the simulation, paramedics and investigators are not blinded. Since our study is held on a high-fidelity manikin, the patients or paramedics incur no risk.

2.3.12. Data collection

2.3.12.1. Data collection methods

Research using simulation has a valid and reliable investigative methodology to study factors affecting human and systems performance in health care has been reviewed⁵⁰. In this project, we will use simulation as an investigative methodology to assess the primary and secondary outcomes described above.

All the actions (ie, primary and secondary outcomes) performed by the paramedics during the scenario will be automatically recorded and stored by the responsive simulator detectors (Leardal SimBaby) and by 3 GoPro Hero 5 Black edition (GoPro Inc) video cameras. The setup of the 3 cameras will be standardized to record at a resolution of 1080p, at 90 frames per second, wide field of view, and with a 16:9 aspect ratio. Cameras position will be standardized. The first camera will be placed in a head strap on the paramedic's head with an inclination of 45° downwards to film the front scene. The second camera will be placed on a tripod in front of the nurse and the manikin, slightly above the head height, with an inclination of 90° downwards to film the place where the drugs will be prepared. The third camera will be placed on a tripod 1 meter away from the paramedic on his or her left (if right-handed) or right (if left-handed) and at the level of the navel to film the scene on the side. All actions performed with PedAMINES will be automatically saved locally in log files for further analysis. The validity and reliability of

the app has been assessed in a prior study⁴⁷. Participants' HR will be recorded during the entire resuscitation scenario with the HR monitor on a Polar A360 watch (Polar Electro Oy). The data will be stored on the wristwatch itself with further analysis being accomplished offline. On-site, the investigators will double-check that the questionnaires are fully and accurately filled.

2.3.12.2. Retention

Our study offers the advantage of being very short in duration, around 60 minutes per paramedic. Therefore, neither follow-up nor retention plans will be necessary. The intervention protocol is highly standardized, and paramedic deviation from protocol in terms of drug preparation is a parameter that is of interest in our study (ie, in terms of medication errors or delays in drug preparation).

2.3.13. Data management

Data collected during the interventions will be entered in EpiData database (EpiData, software v3.1, EpiData Association, Denmark) by the investigators of the study, in anonymised form. To avoid assessment bias, 2 evaluators will then independently review the video recordings. In case of disagreement, a third independent evaluator will help reach a consensus. In order to assess interrater reliability on video reviewing, a kappa score will be calculated.

2.3.14. Statistical methods

2.3.14.1. Statistical method for primary and secondary outcomes

Primary outcome: proportion of medication errors

The proportion of medication errors is the proportion of paramedics committing a medication error. For each type of medication (epinephrine, midazolam, dextrose 10%, sodium bicarbonate), the proportion of medication errors will be reported with 95% confidence intervals (CI, Clopper-Pearson's method) when PedAMINES is used and when the conventional preparation method is used. The difference in proportion of medication errors between preparation methods will also be reported with 95% CI (exact method). The association between the preparation methods (PedAMINES versus conventional method) and the risk of error will be assessed by using a logistic regression model with mixed effects to account for the repetition of measures among paramedics. A random intercept will be introduced in the model. The model will be adjusted for the type of medication since the risk of error can vary across medications.

Secondary outcomes:

a) Proportion of other errors:

The proportions for other types of errors (the choice of drug, air purge in the syringe, labeling of the filled syringe, aseptic errors) will be analyzed in a similar manner as for the primary outcome.

b) Deviation from the correct weight-based dose:

For each of the 4 drugs prepared, errors will be measured by the deviation from the amount of drug taken, the amount of saline solution taken to dilute the drug, the final concentration and the correct weight-based dose. Absolute deviation will be analyzed for each type of medication. The mean (or median) difference in deviation obtained with PedAMINES and with the conventional preparation method will be reported with 95% CI (or inter-quartile interval). A t-test or a Mann-Whitney's test will be used for comparing preparation methods.

c) Time to drug preparation (TDP) and delivery (TDD):

For TDD and TDP, the mean times will be reported with 95% CI for each preparation methods and for each type of medication. The mean difference between preparation methods will also be reported with 95% CI. The association between the preparation methods and TDP and TDD will be assessed by using a linear regression model with mixed effects to account for the repetition of measures among paramedics. A random intercept will be introduced in the model. The model will be adjusted for the type of medication since TDP and TDD can vary across medications.

2.3.14.2. Statistical methods for additional analysis

For the primary and secondary outcomes, logistic regression analyses will be conducted to test a difference in rates of errors between urban EMS (defined as a primary EMS agency in a area populated with 50,000 or more people in the immediate proximity of a tertiary care PED)⁵⁶ and rural EMS (i.e. EMS agency not included within an urban area) with PedAMINES and with the conventional preparation method. In a GEE logistic regression model, an interaction between interventions and urban/rural EMS will be tested to investigate a potential modification of the efficacy of PedAMINES in rural area compared with urban area. Results will also be correlated to the EMS exposition (i.e. total number of emergency calls per year per EMS divided by the number of paramedics working in that EMS). Analyses of primary and secondary outcomes will be conducted in paramedics with more or less than 10 years of experience.

Means and standard deviations will be determined for stress and satisfaction scores (Likert scale) of individuals for each questionnaire item as well as for the UTAUT questionnaire and reported with descriptive statistics. Pearson correlations will be computed between the HR measures obtained with the watch and the scenario phases for each of the drugs and preparation methods used.

2.3.14.3. Analysis population and missing data

Data will be analyzed according to the intention-to-treat principle. Due to the nature of the interventions, we expect to have no missing data. In case of missing data, a complete case analysis will be conducted and no multiple imputations is planned.

2.3.15. Interim analysis

We will not perform interim analyses since our trial has a short duration and no potential serious outcomes.

2.3.16. Access to data

Data will be anonymised and safely stored in triplicate on secured hard disk drives and will be kept in locked cabinets, centralized at the Geneva Children's hospital. Project principal investigators - responsible applicant and co-applicants described above - will have direct full access to the data sets. The project collaborating EMS members will be blinded of any identifying participant information. Only anonymised and summarized data will be submitted as part of the statistical analysis. This method was applied in our prior SNSF study and was 100% reliable and responsiveness.

2.3.17. Dissemination policy

2.3.17.1. Dissemination of study results

The study results will be released to the participating EMS and the general medical community via peer-reviewed journal publications and national / international congresses. The results will be disseminated regardless of the magnitude or direction of effect. An individual collaborating EMS will be authorized to report the data collected from its center alone, provided that he quotes the methods, general results and authorship of the main project.

2.3.17.2. Reproducibility

After publication, we will deliver the full study protocol, deidentified patients data set and statistical code to an appropriate data archive for sharing purposes.

2.4. Study schedule and milestones

Preparation phase	Study year 1	Study year 2
<p>Milestones:</p> <p>Study preparation Duration: 2 months</p> <ul style="list-style-type: none"> - Workshops with EMS heads to prepare study venue in their centers - On-site collaborating EMS visits to prepare the study venue (material and drugs availability, paramedics availability...) - Invitation to paramedics to participate to the study - Wireless manikin SimBaby™ and accessories purchased and available - Data management system ready - Web-based centralized randomization ready (www.sealedenvelope.com) - Transports for amenities and investigators booked - Hotels for investigators booked 	<p>Milestones:</p> <p>Study realization Duration: 12 months</p> <p>Including:</p> <ul style="list-style-type: none"> - All participants enrollment and participation: 1 week per EMS center - Data management: 2 weeks per collaborating EMS - 20% extra time for unexpected incidents (technical incident, paramedics unavailability...) 	<p>Milestones:</p> <p>Data analysis Duration: 4 months</p> <ul style="list-style-type: none"> - Videos reviewing and analysis - Data management <p>Statistics Duration: 1 month, full time</p> <p>Study closure Workshop with study partners</p> <p>Redaction of the study Duration: 5 months</p> <ul style="list-style-type: none"> - Final analysis of endpoints - Manuscripts writing <p>Dissemination Congress and networking</p>
	<p>Number of participants included after 12 months:</p>	<p>120 (full enrollment completed)</p>

2.4.2. Date of completion of preparation phase

01.01.2019

2.5. Importance and impact

EMS will greatly benefit from our project by reducing the overall medication errors and time to resuscitation. By extrapolation and according to Hansen et al.⁴⁰, although survival rate has complex and numerous components, every single minute saved in the preparation of emergency medications thanks to the use of PedAMINES in the prehospital setting will lead to an increase in odds of survival of 9%. Moreover its ease-of-use, small factor size and mobility, customizable list of drugs and its cost-benefits advantages render PedAMINES an absolute essential must have medical application in any EMS. Being able to assess PedAMINES in Swiss EMS is the next step to demonstrate its usefulness in the high-risk and poorly investigated prehospital setting before to deploy the application all over Switzerland in real situations. To date, PedAMINES is the only scientifically validated app to assist medical prescriptions in life-threatening conditions. Our project will also be beneficial to clinical research by offering a common base for further studies on prehospital drugs prescription and medication errors. Because PedAMINES drugs list is customizable, unifying the emergency drugs prescription at the national level will standardize the therapeutic doses used and facilitate further clinical trials on actual or future drugs. Our results will be published in peer-reviewed journals and presented at national and international scientific conferences.

2.6. Commercial interest

The Geneva University Hospitals and some applicants (S.M., J.N.S., F.E., C.L. and A.G.) are the owners of the app PedAMINES that is available on the Google Play Store and the App Store. These applicants, as well as the Geneva University Hospitals, therefore declare a limited direct financial interest to market this app (for R&D only; less than 9.-).

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