PATIENT SAFETY INCIDENTS AND MEDICATION ERRORS DURING A CLINICAL TRIAL: Experience from a pre-hospital randomised controlled trial of emergency medication administration

Ed England[1], Charles D. Deakin[1,2], Jerry P. Nolan[3,4], Ranjit Lall[3], Tom Quinn[5], Simon Gates[6], Joshua Miller[7], Lyndsey O'Shea[8], Helen Pocock[1], Nigel Rees[8], Charlotte Scomparin[3], Gavin D. Perkins[3,9]

[1] South Central Ambulance Service NHS Foundation Trust, Otterbourne, SO21 2RU, U.K.

[2] NIHR Southampton Respiratory Biomedical Research Unit, Southampton, SO16 6YD, U.K.

[3] Warwick Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL, U.K.

[4] Royal United Hospital, Bath, BA1 3NG, U.K.

[5] Kingston University and St George's, University of London, 6th Floor, Hunter Wing, Cranmer Terrace, London, SW17 0RE, U.K.

[6] Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, B15 2TT, U.K.

[7] West Midlands Ambulance Service University NHS Foundation Trust, Brierley Hill, West Midlands, DY5 1LX, U.K.

[8] Welsh Ambulance Services NHS Trust, Swansea, Wales, SA2 8PP, U.K.

[9] Heartlands Hospital, University Hospitals Birmingham, Birmingham, B9 5SS, U.K.

Correspondence to:

Prof Gavin D. Perkins, Warwick Clinical Trials Unit, University of Warwick, CV4 7AL, U.K.

Telephone: +44 24 76 151 738; Email: paramedic@warwick.ac.uk

Keywords: Drug errors, medication errors, clinical trial, drug administration

Total word count: 4085 (including tables)

Abstract

Aim

To assess and evaluate patient safety incidents and in particular, medication errors, during a large multi-centre pre-hospital trial of emergency therapy (PARAMEDIC2), in order to inform and improve future pre-hospital medicines trials.

Methods

The PARAMEDIC2 trial was undertaken across five NHS Ambulance Services in England and Wales with randomisation between December 2014 and October 2017. Patients with an out-of-hospital cardiac arrest unresponsive to initial resuscitation were randomly assigned to 1 mg intravenous adrenaline or matching placebo. Records were reviewed to identify trial medication errors involving documentation and/or clinical protocol errors occurring in trial participants. Causes of medication errors, including root cause analysis where available, were reviewed to identify patterns and themes contributing to these errors.

Results

8,016 patients were enrolled, of whom 4902 received trial medication. 'A total of 331 patient safety incidents was reported, involving 295 patients, representing an overall rate of 3.6% Of these, 166 (50.2%) were documentation errors while 165 (49.8%) were clinical protocol/medication errors. An overall rate of 0-4.5% was reported across all five ambulance services, with a mean of 2.0%. These errors had no impact on patient care or the trial and were all resolved

Conclusion

The overall medication error rate of 1.8 % primarily consisted of administration of open-label adrenaline and confusion with trial medication packs. A similar number of patients had documentation errors. This study is the first to provide data on patient safety incidents relating to medication errors encountered during a pre-hospital trial of emergency medication administration and will provide supporting data for planning future trials in this area.

Abstract word count: 259

Introduction

Clinically significant patient safety incidents (PSI) are defined as any unintended or unexpected incident, which could have or did lead to harm for one or more patients receiving NHS care. Within this classification, medication errors are defined as any PSI where there has been an error in the process of prescribing, preparing, dispensing, administering, monitoring or providing advice on medicines. A 2018 report estimated that 237 million medicine errors occur in England each year, and nearly 28% of these were clinically significant, having the potential to cause moderate or severe harm.[2] In this report, medicine errors were identified at all stages of the medicines use process, the proportions being prescribing (21.3%), transition (1.4%), dispensing (15.9%), administration (54.4%) and monitoring (6.9%). A recent review has identified an overall 10% intravenous medication error rate in hospitals during routine clinical care (101 intravenous medication errors per 1000 administrations (95% CI 84 to 121)), with 32% of the errors overall occurring during medication administration.[3] Paramedic drug prescribing and administration is different from hospital practice, as most paramedics are only authorised to administer drugs under Patient Group Directives and do so without a written prescription. Nevertheless, data for pre-hospital administration is comparable, with error rates of 9-13% reported from two small retrospective studies, one of which was limited by self-reporting.[4 5] Medication errors are likely to be greater during emergency or time-pressured situations, which act to accentuate human factors and compound stress-related errors. Interruptions, multi-tasking, and fatigue occurring in the Emergency Department are all associated with medication administration errors[6 7] and pre-hospital studies have also identified workload and long evacuation times as risk factors for errors.[5] Medicine errors have also been reported in clinical trials, but little is known about the prevalence or types of these errors. Published data mostly relates to hospital-based trials,[8] but medication errors in pre-hospital trials have not been reported.

Patient safety and the integrity of a clinical trial depends on adherence to strict and specific protocols. Deviation from the trial protocol risks patient harm and the integrity of the trial, decreases the power of the study and ultimately jeopardises the ability of the research to deliver meaningful results. The processes for the safe management of medicines in clinical trials are not standardised, and this presents risks.[9] Clinical trials in the pre-hospital environment present specific challenges that are not seen elsewhere and these challenges are likely to be compounded by the administration of medicines in an emergency.

Understanding patient safety incidents that occur in the pre-hospital setting will provide valuable data with which to plan future trials. Information can be used to inform trial protocols and training strategies that minimise medication errors and also to understand the potential for medication

errors to reduce the magnitude of expected treatment effects and thus potentially reduce the power of a trial. The recent UK-based PARAMEDIC2 trial was a randomised, double-blind, trial comparing adrenaline with placebo during out-of-hospital cardiac arrest (OHCA).[10, 11] The aim of the study was to investigate if adrenaline is beneficial or harmful for both short and long-term survival following OHCA. Having recruited 8,014 OHCA patients, it is the largest published pre-hospital clinical trial of an investigational medical product (CTIMP) in cardiac arrest. Trial procedures and oversight resulted in review of every patient recruited to the study, with particular focus on trial medication administration and protocol adherence. This enabled identification of all patient safety incidents and an analysis of the type and cause of each error. This study therefore provided a unique opportunity to also assess and evaluate medications incidents during a large multi-centre pre-hospital trial of emergency therapy, in order to inform and improve future pre-hospital medicines trials.

Methods

The PARAMEDIC2 trial enrolled 8014 patients with OHCA, refractory to initial treatments across from 5 regional ambulance services across England and Wales. Participants were administered either IV adrenaline (4015 patients) or IV placebo (0.9% saline) (3999 patients), along with standard care. Bespoke treatment packs contained 10 pre-filled 3-ml syringes. Each syringe contained a 1 mg dose of adrenaline or 0.9% saline. Treatment packs and syringes contained brief information about the trial and a unique identifying number but were otherwise identical in appearance, thus masking treatment allocation from patients and clinicians.

Clinical staff participating in the trial undertook a training package delivered locally by trial researchers, which involved either participation in either a DVD-based training package, or face-to-face training supplemented by e-learning. The training covered the key elements of the protocol related to enrolment of patients, administration of trial medications and principles of Good Clinical Practice. All those completing training then undertook a local assessment. The detailed methodology has been described previously.[11]

Protocol deviations, violations and serious breaches

Any deviations, or violations of either the trial protocol or Good Clinical Practice (GCP) regulations[12] were reported to the WCTU trial team. These were defined and managed in accordance with the Trial Standard Operating Procedures. All reports were assessed by the trial team on the day of receipt, or the following working day if received on a weekend, and escalated to the Chief Investigator (or their delegate), Quality Assurance Team and WCTU Head of Operations if the non-compliance was a new or exceptional event. All non-compliances, including cumulative numbers, trends and frequency over time, were reviewed at monthly Trial Management meetings. 'The TMG reviewed and allocated each report to one of the following categories of patient safety incident':

- ***Documentation error:*** An unintentional recording error, which upon investigation was not associated with a deviation or violation of the clinical protocol.
- ***Protocol Deviation:*** A change or departure from the protocol and/or GCP that does not result in harm to the study participants or significantly affect the scientific value of the reported results. This may be an unintentional error or a deliberate deviation from the protocol, usually due to clinical reasons.

- ***Protocol Violation:*** A failure to comply with or variance from GCP and/or the final protocol. A violation is a serious non-compliance with the approved protocol resulting from error, fraud or misconduct.
- ***Serious Breach:*** A non-compliance that is likely to affect to a significant degree the safety or physical or mental integrity of the study participants; and/or the scientific value of the study.

All violations and serious breaches were immediately reported to the Sponsor (University of Warwick), and serious breaches were reported to the MHRA within seven days. The Sponsor, WCTU and ambulance service trial teams put in place corrective and preventative actions to mitigate the risk, and these actions were reviewed by the WCTU trial team to ensure all actions had been completed.

In addition to monthly reviews, protocol violations were monitored using graphical plots. The monthly number of violations and the proportion as a percentage of recruitment were plotted. The moving range, defined as the absolute value of month-to-month change, was plotted against the recruitment month. Any out-of-control conditions, defined as outside the pre-specified limits, were investigated for quality control.

Events involving medication errors were further classified (a) and details of controls in place to prevent these from occurring also listed (b) :

- ***Documentation errors***

a) Errors where the medication administration itself was correct but the written record of medication administration was incorrect (e.g. trial pack number was not recorded, the wrong code was recorded on paperwork or the administration of the trial medicines was not notified to the trial team).

b) Investigations were carried out to confirm correct pack numbers and cross checks were made by research paramedics, according to local process, usually including Patient Report Forms (PRFs), drug logs and other local reporting mechanisms (text, voice message system). Retraining was provided where errors were found, together with aide memoirs and reminders via internal newsletters and posters.

- ***Ineligible patients enrolled:***

a) Patients enrolled who did not meet the trial inclusion criteria (Cardiac arrest in out of hospital environment and advanced life support initiated and / or continued by ambulance

service clinician) or those who were enrolled but met one of the exclusion criteria (known or apparent pregnancy, known or apparently aged under 16 years, cardiac arrest caused by anaphylaxis or life threatening asthma, or adrenaline given prior to arrival of ambulance service clinician).

b) Research paramedics checked PRFs to confirm eligibility. A full investigation into cases where confirmed ineligible patients enrolled was carried out, together with a debrief with the attending ambulance crew. Additional labelling was also added to trial drugs to highlight eligibility criteria, with reminders sent to ambulance crew via internal newsletters and posters.

- ***Open label adrenaline given:***

a) Patients in whom standard adrenaline was administered rather than the trial medication.

b) In each case, retraining was provided to individuals concerned and reminders added to posters, aide memoirs and newsletters.

- ***One pack – two patients:***

a) Cases in which one pack of trial medications (containing ten syringes of adrenaline and/or placebo) was administered to two successive patients in cardiac arrest.

b) In each case, retraining was provided to individuals concerned and reminders added to posters, aide memoirs and newsletters.

- ***Two packs – one patient:***

a) Cases in which two trial packs were opened at a cardiac arrest and medications from both packs potentially administered to the patient.

b) Additional trial drug labelling.

- ***Expired pack used:***

a) Cases in which time-expired medication was administered. (The decision to categorise the use of an expired pack as a deviation or violation was based on whether the pack was used within the 12-month shelf life.)

b) Advice was sought from the manufacturer's Qualified Person to confirm stability of product. Clear recall process of trial drug in pre-hospital setting. Packs unaccounted for were tracked by research paramedics, alerts were made to regional managers, and a process for reporting expired packs to research paramedics was put in place.

- ***Wrong pack:***

a) Patients where medication administered was not taken from the allocated trial pack. (A pack not allocated by the randomisation process).
b) In each case, retraining was provided to individuals concerned and reminders added to posters, aide memoirs and newsletters.

All protocol medication non-compliance events occurring during the study period were collated and analyzed at the conclusion of the study.

Results

Medication errors

There were 331 medication errors among the 8106 trial patients over the three-year study period. This total included a subset of 166 documentation errors. An overall rate of 0 - 4.5% was reported across all five ambulance services, with a mean of 2.0%. These errors had no impact on patient care or the trial and were all resolved. Medication errors classified as 'missing' refer to drug trial packs that went missing, so it was not possible to determine whether the error related to adrenaline or placebo.

Medication Error	Deviation			Violation			Serious breach			Not a deviation/violation		
	Missing	Placebo	Adrenaline	Missing	Placebo	Adrenaline	Missing	Placebo	Adrenaline	Missing	Placebo	Adrenaline
Documentation errors	0	0	0	0	0	0	0	0	0	3	75	88
Ineligible patients enrolled	0	0	0	5	3	8	1	0	1	5	5	10
Open label adrenaline given	1	11	7	0	16	24	0	0	0	0	0	1
One pack – two patients	0	2	6	0	0	0	0	0	0	0	0	0
Two packs – one patient	0	1	3	0	8	2	0	0	0	0	0	0
Expired pack used	0	3	3	0	1	2	0	0	0	0	0	0

Wrong pack documented	0	0	0	0	0	0	0	0	0	0	8 (42.1%)	11 (57.9%)
Other	0	18	17		1	2	0	0	0	0	9	10
Not trained	0	0	0	0	12	7	0	0	0	0	0	1

Table 1: Medication errors (Total recruits = 8106)

Inadvertent recruitment of patients who met exclusion criteria are listed in Table 2, together with the root cause analysis.

Reason	**N=**	**Root cause analysis**		
		Exclusion not evident at time of enrolment	Clinician error	Drug prepared by non-trial trained staff
Pregnancy	1	1*	0	0
Anaphylaxis	6	3*	3	0
Asthma	10	5**	5	0
Under 16 years	2	1		1

* Patients withdrawn and open label adrenaline administered when clinician became aware of exclusion. ** 4 patients withdrawn as possibility of asthma identified after enrolment but during on-going treatment.

Table 2: Ineligible patients enrolled

In 57 patients, open-label adrenaline rather than trial medication was administered at the initial cardiac arrest when the patient was entered in to the trial. The reasons for open-label administration are listed in table 3.

Reason	**n=**
Trial pack finished and more adrenaline needed	14
Re-arrest	5
Other clinician took over/multiple providers	31
Post-ROSC adrenaline then re-arrest	4
Adrenaline for asthma then trial med	1
Two trial packs given then recognised error so adrenaline given	1
Reason unknown	1

Table 3: Open label adrenaline administered to patients enrolled in trial

The total number of protocol violations occurring each month during the trial period are shown in Figure 1, both as a total and as a % of monthly recruitment.

Discussion

A total of 331 errors were reported involving 295 patients, during the recruitment and enrolment of 8106 trial patients, representing an overall error rate of 3.6%.with some patients experiencing more than one event. Of these, 166 (50.2%) were documentation errors whilst 165 (49.8%) were clinical protocol/medication errors. This is the first reported analysis of medication errors during a clinical trial in the pre-hospital emergency environment, and provides data to establish a baseline of the prevalence and types of errors that may occur when conducting medication trials in this setting. The medication errors we describe consist of those occurring as a result of medication administered during the stress of emergency and time-critical therapy, compounded by the additional complexities of medication administration as part of a trial protocol. Errors occurred at all stage of medication administration, but were particularly common in relation to the retrospective documentation, and accounted for approximately half of all errors. Administration of open-label adrenaline was the largest single cause of medication-related error (18.5%), but confusion about the actual trial medication packs (expired pack, multiple packs opened etc) accounted for almost as many errors (15.4%). Although trial exclusion criteria varied from the usual indication for adrenaline administration during cardiac arrest, which had the potential to cause confusion, relatively few incidents of enrolment of ineligible patients were reported (19/324; 5.9%). This low rate may have been achieved by having a large, clear label attached to the trial medications listing exclusion criteria.

The training package for paramedics taking part in the trial included emphasis on the equivocal evidence for adrenaline, particularly in relation to long-term neurological outcomes. This focus on explaining the rationale for the trial to paramedics may have contributed to the relatively low rates of intentional non-compliance than seen in previous trials.[13] Greater rates of non-compliance were seen when clinical management was taken over by those not familiar with, or trained in, the trial. On occasion, senior staff not trained in the trial protocol overrode the decision of trained staff in the decision to recruit a patient to the trial. Of the 60 cases of medication errors when open label adrenaline was administered, 19 cases occurred when non-trial clinicians became involved in the medication decision-making process once trial enrolment had occurred, resulting in a deviation of the trial protocol.

Exclusion criteria in clinical trial are usually due to regulatory / trial based reasons or because there is a contraindication or rationale for why a particular patient group should not be involved. In PARAMEDIC2 we excluded patients for regulatory / trial related reasons who were known to be pregnant or aged less than 16 years. The rationale for excluding these groups was the infrequency of

cardiac arrest events in these populations, different causes and outcomes of cardiac arrest, insurance considerations and in addition for children, different models for obtaining consent and different tools to record neurological outcomes. Patients with suspected anaphylaxis were excluded due to the theoretical benefits of mast cell stabilising effects of adrenaline,[14] although no clinical trial evidence exists to support adrenaline use during cardiac arrest in this setting.[15] The literature in relation to safety and effectiveness of adrenaline in cardiac arrest due to asthma is also lacking. Indirect evidence suggests the potential for both benefit and harm in this group.[16] Given the potential for overlap in the clinical presentation of asthma and anaphylaxis, and relative infrequency of this type of cardiac arrest, the trial team took the pragmatic decision to exclude this patient group. Enrolment of ineligible patients nevertheless requires careful review and scrutiny. In PARAMEDIC2 a root cause analysis was undertaken for each case and corrective and preventative actions taken. Across these detailed reviews two key themes emerged (1) failure to recognise that the patient had the condition at the time of enrolment (2) failure to remember the specific exclusions at the time of enrolment. In these cases, the existing preventative measures (protocol training, presence of trial exclusion criteria on the outside of the treatment packs and labels on the syringes, were insufficient to prevent enrolment in error. Whether alternative approaches such as the use of checklists, or verbal challenge, already proven in the surgical environment,[17] would be practicable and reduce error remains to be determined.

With regular exposure to the trial protocol, we believed that the rate of medication errors might have declined as the trial progressed. However, the majority of paramedics respond to no more than 1-2 cardiac arrests annually,[18] so individual exposure to the trial was relatively infrequent. This may explain why there was little change in the overall rate of medication errors over the duration of the trial (Figure 1). There was a wide variation in errors occurring across the five ambulance services participating in the study, both in terms of type of error and absolute numbers. Overall error rates between ambulance services ranged from 1.7% to 7.1%. This variation in error rate between ambulance services was represented in errors across all categories. Errors between ambulance services are likely to reflect a variation in internal policies and procedures, composition of clinical resources on scene, variation in refresher training in resuscitation, cultural approaches to participating in research, or a different reporting culture.[19] The higher rate of reporting from one ambulance service may reflect a higher error rate, an increased level of awareness of safety or a more open and transparent reporting culture. The participating ambulance services had agreed different local processes to deliver the trial. This was designed to help the trial integrate with local established logistical processes. Unfortunately, it is not possible to identify whether these different

processes had an impact on these subsequent medication errors. A systematic review of medication errors in adult intensive care documented variation in local processes but did not find evidence to support the benefit of any particular intervention to reduce medication errors; these included changes in work schedules, modes of education, protocols and guidelines and support systems for clinical decision making.[20]

Factors specific to the clinical setting and the treatment being administered may reduce trial protocol compliance and contribute to errors. Twelve of the 60 open label adrenaline administered errors were attributed to a 'chaotic' environment. This is consistent with reports that clinical error rates in the emergency department increase almost threefold when physicians are interrupted.[6] Interruptions are often cited as a problem in medication safety, particularly in relation to nurses administering medication,[21] though these errors are generally related to the time of administration of the medicine and the rate of administration,[7] both of which are not applicable to this study.

This report presents a summary of cases where patients did not receive the trial medication as anticipated in the trial protocol, which has occurred as a result of both medication errors where actions are intended but not performed, and deviations from trial protocol where the treating clinician considered it in the patient's best interest (correctly or otherwise) to deviate from the trial protocol. Considering the frequency with which medication errors occur, the potential for patient harm and the impact on the validity and integrity of research studies involving medication administration, there is surprisingly little published in the literature about medication errors. A number of studies have examined factors associated with medication errors.[22] Some are general factors associated with all prescribing (e.g. lack of therapeutic training, inadequate drug knowledge and experience, prescribing systems that allow for human error, confirmation bias etc), but others are factors specifically relating to time-critical, emergency situations which together can cause cognitive overload. Workload and time pressures, distractions and interruptions, lack of standardized protocols and procedures, and insufficient resources are all major contributors to the risk of medication errors.[22] The pre-hospital environment also adds further contributory factors not present in the hospital environment. The physical environment was among the top five factors contributing to medication errors.[23]. and challenges with the physical work environment (e.g., lighting, temperature and ventilation) are particularly prevalent when dealing with patients in cardiac arrest.

Overall, the number of medication errors of 3.6% reported in this trial is relatively low. A review of studies of medicine administration errors, mainly from the US and the UK found a median error rate

of 8.0% (5.1-10.9%).[24] More errors were observed for the intravenous route (53.3%) where each dosing error could accumulate more than one error. A previous study reporting medication errors during a cancer medication trial similarly reported that approximately half of all medication errors did not involve medication delivery to the patient.[25] An observational study of prescribing errors by emergency physicians in Australia found on average 0.4 clinical prescribing errors per patient and 2.6 legal/procedural errors per patient, with 60% of medicine prescriptions having 1 or more errors.[6] Most errors were insignificant (94.2%) and the remainder were of moderate severity. The number of errors reported in this Australian study was significantly less, mostly likely because the trial involved a short and very specific patient care episode. The relatively few errors reported in this study may be in part because only one patient was being managed at a time, using a limited number of medicines, as previously reported.[4] Additional training for trial paramedics, together with anticipated close observation and scrutiny of the trial patients may also have contributed to fewer errors. There may also be underreporting of procedural errors, as it appears that most were reported by one of the five ambulance services involved in the study. Previous medicine trials have found that the majority of medication errors are corrected before the medication is administered to the patient, or they do not result in patient harm.[25] This is consistent with our findings. The most common cause of error was not following the procedure or the protocol, which may be both due to a lack of understanding or an intentional decision,[26] compounded by the infrequent exposure to OHCA by individual paramedics.

The causes and contributory factors to medication errors should be considered during the trial design process. Interruptions during pre-hospital care should be minimised, but the pre-hospital setting may make this difficult. Communication tools should be considered because good communication plays a role in reducing medication errors. This should include communication with clinicians who are present but who have not been trained in, or are unaware of, the trial. Previous studies have documented errors related to fatigue, clinical workload and stress, compounded by interuptions to adminstration of trial medication and multi-tasking. It is clear therefore that improvements in drug error rates will be achieved by ensuring cardiac arrest teams are well reheared and practiced in the delivery of this protocol-driven task. The move towards pre-hospital electronic recording of clinical care is likely to reduce overall workload and improve documentation errors, ensuring more accurate recording of drug administration. Future medication trials should routinely report medication errors so that trial design can be continually improved. Consideration should be given to standard methods of error classification, as this will enable comparison between sites and between trials. However, there is some inconsistency with the published classification of

errors which could also be addressed in future research. Clinicians must be encouraged to report all errors and near misses, so that learning can take place.

Conclusion

In this pre-hospital randomised clinical trial of 8106 patients, we documented a relatively low overall medication error rate of 1.8 %. Errors in relation to documentation accounted for approximately half of all errors, with the remainder primarily consisting of those relating to administration of open-label adrenaline and confusion with trial medication packs. There was little change in the overall rate of medication errors over the four-year duration of the trial, possibly due to the relative infrequency with which individual paramedics enrolled patients into the trial. This study is the first to provide data on medication errors encountered during a pre-hospital trial of emergency medication administration and will provide supporting data for planning future trials in this area.

Acknowledgements (If any)

We thank all those involved in the original PARAMEDIC2 trial from which this data was extracted. In particular, we thank London Ambulance Service NHS Trust, North East Ambulance Service NHS Trust, South Central Ambulance Service NHS Trust, Welsh Ambulance Service NHS Trust, West Midlands Ambulance Service NHS Trust, members of the Trial Steering Committee and Data Monitoring Committee and the University of Warwick Clinical Trials Unit.

Authors' Individual Contributions:

All authors contributed to the design and implementation of the research, and to the analysis and interpretation of the results. EE and CD led the writing of the manuscript with input from all authors. The trial statisticians (RL, SG) collated and analysed the trial data.

Funding Information

The original PARAMEDIC2 trial from which this data is extracted was funded the National Institute for Health Research Health Technology Assessment Programme (12/127/126)

Conflict of Interest

All authors report the grant from National Institute for Health Research related to the PARAMEDIC2 study. All authors declare no other COI.

References

1. NHS England and Medicines and Healthcare Products Regulatory Agency. Patient Safety Alert: Supporting Information. Improving medication error incident reporting and learning. 2014. https://www.england.nhs.uk/wp-content/uploads/2014/03/psa-sup-info-med-error.pdf Accessed 30th July 2019.
2. Elliott R, Camacho E, Campbell F, Jankovic D, Martyn St James M, Kaltenthaler E, Wong R, Sculpher M, Faria R, (2018). Prevalence and Economic Burden of Medication Errors in The NHS in England. Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. http://www.eepru.org.uk/prevalence-and-economic-burden-of-medication-errors-in-the-nhs-in-england-2/ Accessed 30th July 2019.
3. Sutherland A, Canobbio M, Clarke J, et al. Incidence and prevalence of intravenous medication errors in the UK: a systematic review. *European Journal of Hospital Pharmacy* 2018:ejhpharm-2018-001624.
4. Lifshitz AE, Goldstein LH, Sharist M, et al. Medication prescribing errors in the prehospital setting and in the ED. *Am J Emerg Med* 2012;30(5):726-31.
5. Vilke GM, Tornabene SV, Stepanski B, et al. Paramedic self-reported medication errors. *Prehosp Emerg Care* 2007;11(1):80-4.
6. Westbrook JI, Raban MZ, Walter SR, et al. Task errors by emergency physicians are associated with interruptions, multitasking, fatigue and working memory capacity: a prospective, direct observation study. *BMJ Qual Saf* 2018;27(8):655-63.
7. Westbrook JI, Woods A, Rob MI, et al. Association of interruptions with an increased risk and severity of medication administration errors. *Arch Intern Med* 2010;170(8):683-90.
8. Moon JY, Lee Y, Han JM, et al. Effects of pharmacist interventions on reducing prescribing errors of investigational drugs in oncology clinical trials. *J Oncol Pharm Pract* 2019:1078155219834723.
9. Brown JN, Britnell SR, Stivers AP, et al. Medication Safety in Clinical Trials: Role of the Pharmacist in Optimizing Practice, Collaboration, and Education to Reduce Errors. *Yale J Biol Med* 2017;90(1):125-33.
10. Perkins GD, Ji C, Deakin CD, et al. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2018;379(8):711-21.
11. Perkins GD, Quinn T, Deakin CD, et al. Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): Trial protocol. *Resuscitation* 2016;108:75-81.
12. https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials. Accessed 28th November 2019.
13. Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation* 2011;82(9):1138-43.
14. Tanno LK, Alvarez-Perea A, Pouessel G. Therapeutic approach of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2019;19(4):393-401.
15. Sheikh A, Shehata YA, Brown SG, et al. Adrenaline for the treatment of anaphylaxis: cochrane systematic review. *Allergy* 2009;64(2):204-12.

16. Franchini S, Marinosci A, Cicenia G. Emergency treatment of asthma. *N Engl J Med* 2010;363(26):2567; author reply 68-9.

17. Pugel AE, Simianu VV, Flum DR, et al. Use of the surgical safety checklist to improve communication and reduce complications. *J Infect Public Health* 2015;8(3):219-25.

18. Deakin CD, King P, Thompson F. Prehospital advanced airway management by ambulance technicians and paramedics: is clinical practice sufficient to maintain skills? *Emerg Med J* 2009;26(12):888-91.

19. Patient Safety Incident Reporting (in the NHS). https://www.england.nhs.uk/2015/09/patient-safety-reporting/ Accessed 1st August 2019.

20. Manias E, Williams A, Liew D. Interventions to reduce medication errors in adult intensive care: a systematic review. *Br J Clin Pharmacol* 2012;74(3):411-23.

21. Bower R, Jackson C, Manning JC. Interruptions and medication administration in critical care. *Nurs Crit Care* 2015;20(4):183-95.

22. Medication Errors. Technical Series on Safer Primary Care. World Health Organisation. 2016 ISBN 978-92-4-151164-3.

23. Lawton R, McEachan RR, Giles SJ, et al. Development of an evidence-based framework of factors contributing to patient safety incidents in hospital settings: a systematic review. *BMJ Qual Saf* 2012;21(5):369-80.

24. Keers RN, Williams SD, Cooke J, et al. Prevalence and nature of medication administration errors in health care settings: a systematic review of direct observational evidence. *Ann Pharmacother* 2013;47(2):237-56.

25. Kane MP, Fessele K, Gordillis-Perez J, et al. Medication safety in cancer clinical trials: An analysis of medication error reports at a comprehensive cancer center. *Journal of Clinical Oncology* 2016;25, no. 18_suppl (June 20 2007) 6547-6547

26. Heneka N, Shaw T, Rowett D, et al. Opioid errors in inpatient palliative care services: a retrospective review. *BMJ Support Palliat Care* 2018;8(2):175-79.