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A national evaluation of harm associated with patient safety incident reports related to the provision of parenteral nutrition to patients using a national incident reporting system

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Abstract:

Background
Parenteral nutrition (PN)-related patient safety incidents have been associated with harm. Large scale studies are scarce and little is known about contributory factors. This study evaluated PN-related incident reports that described harm using a national database.
Materials and Methods
A retrospective evaluation of incident reports involving PN in England and Wales, reported to the National Reporting and Learning System (NRLS) between April 2015-March 2020. Quantitative analysis was used to describe frequency by degree of reported harm and incident characteristics. Content analysis was undertaken to understand contributory factors for reports related to moderate/severe harm, or death.
Results
12,907 incident reports were identified. After screening 2242 were evaluated; 1879 (83.8%) reported no harm, 309 (13.8%) low harm, 47 (0.02%) moderate harm, 4 (0.002%) severe harm, 3 (0.001%) deaths. Most reported age group, medication process and error category was neonates (<28 days) (n=570/1923, 29.6%), administration (n=1126/2242, 50%), and omitted medication/ingredient (n=291/2242, 13%), respectively. Content analysis of reports related to moderate/severe harm and death revealed patient age <1 year, dependence on home parenteral nutrition (HPN), co-morbidities and staff mistakes as contributory factors.
Conclusions
This is the first evaluation of PN-related incident reports in England and Wales to our knowledge. We demonstrated a low frequency of reports related to moderate or severe harm or death. More incidents were reported for neonates and during the administration processes. To reduce harm, systems/procedures that reduce errors in high-risk patients (e.g., neonates, HPN patients) need to be established within organizations. Database limitations of voluntary reporting systems were recognized.

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Abbreviations

GDPR General Data Protection Regulation; HPN Home parenteral nutrition; HRA Health Research Authority; ILE Lipid injectable emulsion; NCC MERP National Coordinating Council for Medication Error Reporting and Prevention; “organization removed”; “database name removed”; PN Parenteral nutrition; WHO World Health Organization

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1. Introduction

Parenteral nutrition (PN) is a multi-ingredient medicinal product administered intravenously when nutritional requirements cannot be met using the gastro-intestinal tract. It contains macro and micronutrients needed to sustain life, comprising of over 40 ingredients. This complexity raises concerns about physicochemical stability. It can be used short term in hospital, but also be given as home parenteral nutrition (HPN) for long term conditions. Indications for PN include inadequate or unsafe oral/enteral nutrition, or due to a non-functioning, inaccessible or perforated gastro-intestinal tract.[1]

PN is widely regarded, but not unanimously, as a high-risk medicine.[2,3] Its speciality use may contribute to lack of familiarity with products and procedures among healthcare professionals who does not use PN in their daily practice. The World Health Organization (WHO) do not recognise PN as a high-risk medicine,[4] however in the USA PN is broadly accepted as a high-risk medicine in acute care.[5-7] Prescribing, compounding and administration errors related to PN are believed to be multifactorial, related to lack of training and human error.[8] A "patient safety incident" is defined by the "organization removed" in "Country Y" and "Country Z" as any unintended or unexpected incident which could have, or did lead to harm.[9] In "Country Y" and "Country Z", the "database name removed" is the national repository for patient safety incident reporting data used by the "organization removed".

A recent review of the literature suggest PN-related incidents occurr during any part of the medication process and in all patient age groups, although children may be more susceptible to harmful outcomes.[10] Incident types were divided into the following categories; microbial contamination,[11-14] venous access incidents involving extravasation,[15-19] incidents related to specific PN-components or the compounded bag.[20-22] Lipid injectable emulsion (ILE), glucose, electrolytes and micronutrients components of PN have been involved in case reports.[23-28]

A national review of PN-related incidents in the USA reported over two years, in all age groups was published in 2017.[29] There were 1311 incidents, of which 19 (1.4%) caused harm. ILE was the most frequently occurring PN component associated with reported incidents (257/1311, 20%). The most common medication process was administration (497/1311, 38 %), the most common error type, was improper dose/quantity (541/1311, 41%). Incidents were not sub-divided into patient age groups. This study suggested a low incidence of harmful

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events associated with PN. Other prevalence studies also showed a low incidence of harm, although were either focussed on a specific age group, were local studies or not focussed exclusively on PN.[30-32] Large scale studies are scarce, and there is little understanding of contributory factors associated with harmful events. The "database name removed", like other incident reporting systems, include headings where free text descriptions of what happened, actions preventing reoccurrence and apparent causes can be added by the reporter. Analyzing the information reported in these sections can support learning and developing interventions based on findings to reduce/eliminate future events.

The aim of this study was to evaluate PN-related patient safety incident reports related to harm in "Country Y" and "Country Z" using a national database. The objectives were, (1) to evaluate PN-related incident reports by category; patient age group, location, speciality, medication process and medication error category, (2) to assess relationships between reported categories, and (3) to qualitatively analyze free-text description for PN-related incident reports that were related to moderate/severe harm or death, to provide an insight into contributing factors.

2. Methods

2.1. Design

This retrospective cross-sectional study was an evaluation of medication incident reports involving PN reported to the "database name removed", the national incident reporting system in "Country Y" and "Country Z". Qualitative analysis using content analysis was conducted on incident reports that were categorized as moderate/severe harm or death. The primary outcome was the assessment of harmful incident reports related to PN to understand the level of harm associated with these incident reports. Secondary outcome measures to enable further detailed evaluations included the following categories; patient age, location, speciality, care setting, medication process, medication error category, staff reporter type.

2.2. Data extraction

Data extraction required approval by the "database name removed" and careful consideration to capture all relevant incidences. Relevant incident reports occurring between April 2015 and March 2020 were retrieved by the "database name removed". This 5-year period was selected to capture an accurate reflection of current incidents, excluding incidents related to outdated practices.

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Formulation of the final search criteria involved an iterative process between the primary investigator (PM) and the "database name removed" data analyst team to obtain a dataset of relevant incident reports. Full details of the agreed search terms and sampling are included as supplementary material. Broad name and brand name search terms were agreed upon with the "database name removed" data analyst team. A database search of the broad names and brand names was carried out by the "database name removed" data analyst team. All entries were supplied for analysis. A database search of the broad names or brand names was also conducted. For these entries all incident reports resulting in moderate/severe harm or death were provided, and a random sample of incident reports resulting in low (23.1%) or no (16.8%) harm. The search was confined to patient safety incident reports related to PN reported under the NLRS medication incident category. Patients of all age groups and all care settings were included. Incident reports of all degrees of harm and all medication processes were included in the analysis.

2.3. Data analysis

Irrelevant entries were identified by the primary investigator using the approved drug name field to highlight incident reports caused by other drugs, and then removed if not related to PN. Any incident reports with incomplete approved drug name entries were manually checked. During analysis, coding discrepancies were noted by the primary investigator, although no entries were changed. IBM® SPSS® Statistics (version 26) was used for quantitative analysis. Full details of the fields used in the analysis are included as supplementary material.

Descriptive statistics were used to describe patient demographic data. Statistical analysis was not appropriate for this observational data. Data for adults (≥18 years) and children (0-17 years) were combined to enable comparison for medication process and degrees of harm.

Content analysis of free-text data in incident reports related to moderate/severe harm or death was performed to uncover meaningful patterns.[33] The free-text data within the "database name removed" fields for descriptions of what happened, actions preventing reoccurrence and apparent causes were read as a whole and analyzed to form themes relating to incident types, contributory factors and outcomes. This initially involved formation of codes from the free-text. Codes can be described as a word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute for a portion data.[34] Codes were then grouped to form *themes* to express underlying meanings within the text.[35] During

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content analysis incident reports not related to PN, were removed from the analysis. They were not removed from all analysis as this level of scrutiny was not applied to those reported as no/low harm.

2.4. Ethical considerations

Ethical approval by the "XXXXXX Institution", "Ethics committee removed" (XXXXX: 60567) for a service evaluation was obtained for this Master's study. Approval for this service evaluation was also obtained from "the Hospital" (SEV/0299). "National Ethics committee name removed" approval was not required. Data files extracted from the "database name removed" database were password protected and accessed only from the protected hospital server to ensure secure data storage. The data retrieved from "database name removed" were anonymous however "national regulation name removed" was followed in line with "database name removed" requirements.[36]

3. Results

The search of selected PN terms identified 12,907 incident reports between April 2015 and March 2020, of which 2339 incident reports were supplied by the "database name removed" team. All incident reports related to moderate and severe harm or death were provided. For incident reports related to low or no harm, a sample was provided with consideration to feasibility for a master's project. After screening, 2242 reports were included in this evaluation (Figure 1). There were 354 reports with blank fields for *approved drug name* or an entry such as "?" or "-". These were manually checked and 14 reports were removed. Seventeen duplicate reports with the same incident number were also removed.

Of the 2242 incident reports, there were 1879 incident reports that had been reported to have caused no harm, 309 low harm, 47 moderate harm, 4 severe harm and 3 deaths.

3.1. Characteristics of incident reports

The highest number of incident reports involved neonates (<28 days) (n=570/1923, 30%), followed by children between 1 month and 1 years old (n=397/1923, 21%) (Figure 2).

Table 1 shows the breakdown of incident reports by degree of reported harm and patient age group, location and speciality. All incident reports occurred within an acute/general hospital care setting. Four incident reports were reported to have occurred in community hospitals, however this was found to be a reporter error. The location for the majority of the incident reports were within in-patient ward areas (n=1780/2236,

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79.6%), followed by support services (n=264/2236, 29%), within which 96% (n=254/264) were reported in pharmacy. Medical specialities were the most reported speciality group (n=743/2242, 33%). Subheadings under this speciality included gastroenterology, nephrology, neurology, respiratory, oncology, general medicine and neonatology. Neonatology was also listed as a subheading under children's specialities, hence variations in reporting specialities were noted. Several inconsistencies were noted when reviewing the data e.g., 1198 incident reports were in children aged under 18 years, yet only 210 reported under children's speciality, suggesting reporter differences when assigning locations and/or specialities. Incident reports were also categorized by medication process and medication error category (Table 2). For medication process the highest number of incident reports were described as administration/preparation in clinical area (n=1126/2242, 50%), and was also the most frequent across all reported degrees of harm. There were seven incident reports under supply or use of OTC medicines category. PN is a prescription only medicine in the "Country X", therefore these were likely reporter errors. The most reported medication error category was omitted medication/ingredient (n=291/2242, 13%).

3.1. Patient age groups and degree of reported harm

The number of reported moderate/severe harm and deaths in the adult and children age groups were similar. In children there were 25 incident reports, of which two were related to severe harm, and two deaths. In adults there were 23 serious incident reports, of which one was related to severe harm and one death.

3.2. Patient age and medication process

The proportion of incident reports within administration/preparation in clinical area were similar (52%) for children and adults (Table 3). Children had a higher proportion of prescribing incident reports than adults (15% and 11% respectively), although adults had a higher proportion of incident reports within preparation from all locations/dispensing from pharmacy than children (25% and 18% respectively).

3.3. Medication error categories within medication process

For most error categories, administration/preparation in clinical area was the most frequently reported process (Table 4). The most frequently reported error category was omitted medication/ingredient within administration/preparation in clinical area (n=142/291, 49%) and preparation from all locations/dispensing

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from pharmacy process (n=96/493, 19%). For prescribing the most frequently reported error category was wrong/unclear dose or strength (n=67/305, 22%).

3.4. Staff reporter type

Staff reporter type was only reported in 0.94% (n=21/2242) of incident reports and left blank in the rest. Staff nurses/midwives/health visitors reported most of these incident reports (n=13/21, 62%).

3.5. Content analysis

There were 54 incident reports related to moderate/severe harm or death. On closer inspection, it was discovered that one was not a PN incident and therefore excluded from content analysis.

There were eight overarching themes which described the incident reports (Table 5). The most common was administering medicines. In addition to PN, insulin, glucose and electrolyte solutions were also cited as being involved. The most frequent incident type within this theme was adverse events from administration, which was related to extravasation of PN in all cases.

Patient factors were the most frequently occurring contributory factor theme (Table 6). The majority of these were patient dependent on HPN. HPN patients were often also patients with co-morbidities. In addition to nutrients, they would require strict fluid and electrolyte management, and missed infusions were reported to have severe consequences of acute kidney injury, deranged blood glucose control and hypokalaemia. Most HPN incident reports were related to dispensing or supply of infusions. Being at home without access to immediate medical intervention could make these patients more vulnerable if infusions are missed. PN extravasation was the most frequent incident reported in children less than 1 year, and over half of these were neonates. Organization was the second most frequently occurring theme. The most frequent factor within this theme was service failure of an external company due to a national incident and affected HPN patients. Staff factors were the third most common theme, with mistakes being the most frequent contributory factor. The majority of these were administration incident reports. The fourth theme was equipment and venous access devices used to infuse PN was a common contributory factor.

Themes relating to patient outcomes are displayed in Figure 3. Patient harm included clinical outcomes such as pathophysiological/disease related, patient injury or patient death. Pathophysiological/disease related outcomes included fluid/electrolyte disturbances and blood glucose control. All reported outcomes were PN

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extravasation. There were three incidents reported as death, two of which involved HPN patients, one contributed to delivery failure in an adult patient and one was a compounding incident in a child aged 12-17 years. The third death was contributed to by an overdose of PN due to a mistake in infusion rate in a neonate. The non-clinical outcomes described inconvenience to patients but are also a burden on healthcare organizations, through repeated tests/procedures or additional treatment and unplanned hospital admissions which were reported.

4. Discussion

4.1. Main findings

To our knowledge, this is the first national evaluation focussed on PN incident reports across all patient ages in "Country Y" and "Country Z". The "database name removed" database search of PN terms returned 12,907 incident reports over a 5-year period, of which only 54 reported moderate/severe harm or death. Although this represents raw data before screening, only 0.4% of incident reports were related to moderate/severe harm or death. The dataset of 2242 incident reports included a sample of no/low harm incident reports and all incident reports of moderate/severe harm or death. On examination, only 53 incident reports were related to moderate/severe harm or death. Snijders et al. [30] and Storey et al. [29] reported that 1% (n=3/304) and 1.4% (n=19/1311) of PN-related incidents respectively, caused significant harm. Both studies used national reporting databases, although Snijders et al. [28] looked only at incidents in neonatal intensive care units. Local observational studies by Narula et al. [32] and Sacks et al. [31] reported that 6% (n=3/46) and 8% (n=6/74) of PN-related incidents respectively, caused significant harm. Narula et al. [30] reported data in a pediatric centre, and Sacks et al. [29] reported incidents in all age groups. In comparison, the "database name removed" data revealed a large number of incident reports involving PN. The prevalence and populations cannot be compared, however our study demonstrated a lower proportion of incident reports related to moderate/severe harm or death than the studies mentioned above. This higher proportion could be related to differences in reporting to national and local databases, or assigning degree of harm. Snijders et al. [30] used a similar approach to the "database name removed" to describe degrees of harm, ranging from no harm to death, where significant harm was described as moderate/severe or death. The other three studies used the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index to assign

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harm to incidents.[37] This index uses 9 categories (A to I) to describe levels of harm, and significant harm in these studies were incidents categorized grades E to I (temporary harm to death).

Overall, 62% of incident reports were in children, with incident reports in neonates occurring most frequently. Infants under 1 year were also highlighted as a commonly occurring contributory factor in incident reports of moderate/severe harm or death. This could be due to complexity of weight-based dosing or vulnerability due to the under-developed defence mechanisms and developing organs.[38,39] Within the adult group, most incident reports were reported in the 66-75 years age group. This requires further investigation and may be related to a combination of factors such as co-morbidities and volume of PN used in this patient population, e.g., post-operative surgical complications requiring short-term PN or eligibility for HPN. There were a similar number of incident reports of moderate/severe harm or death between adults and children for the sample of incident reports we analyzed. This was based on the assumption that this sample was representative of the whole dataset of incidents. This differs from published literature which suggests children are more susceptible to harm than adults from medication errors.[38,39] This may be related to the multifactorial nature of contributory factors found in this evaluation, such as the influence of a national HPN incident.

The single most common medication process reported for both adults and children, and for all reported degrees of harm was administration. This was in agreement with the study by Storey et al.,[29,39] and several published case studies.[16-18,24,27,28] In the "Country X" it is recommended that additions to PN bags, including multi-chamber bags, only occur in the pharmacy aseptic unit.[40] This may vary in other parts of the world, and studies have described the supplementation of micronutrient and/or electrolyte to multi-chamber bags in a clinical setting.[41-43] This difference in practice should be considered when comparing incident rates in other countries. Extravasation injuries, patient age less than one year and venous access devices were predominant factors for administration incident reports of moderate/severe harm or death. These incident reports were found to be the result of insufficient monitoring or inappropriate venous access devices, e.g., peripheral intravenous route used for high osmolarity PN that should only be infused centrally. Extravasation injuries in infants due to PN has been recognised in several case reports, and has also been highlighted by this study. [15-18] Incident reports related to the wrong dose being administered were frequently related to a mistake being made by healthcare staff, although were difficult to categorize further due insufficient information.

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The proportion of incident reports that had occurred during the administration process in children was similar to adults. The higher proportion of incident reports for children in the prescribing process may be related to the complexity of PN prescribing in children.[39] The higher proportion of incident reports for adults within dispensing process was in agreement with the results by Bateman et al.[44] Further investigation of contributory factors focussing on dispensing incidents is required.

Age under one year was identified as a contributing factor together with venous access devices and mistakes. The added complexity of separate ILE and non-lipid PN infusions creates an area for potential errors in these patients. Further development of all-in-one PN products for this age group could remove the need for separate ILE and non-lipid PN infusions. PN when used in neonates and infants under one year should be treated as a high-risk medication, accompanied with double-checking procedures during set-up and the infusion period. Stringent venous access protocols that comply with national guidance for neonates may also reduce PN extravasation injuries.[45]

The top five medication error categories were, omitted medication, wrong quantity, wrong dose, wrong medicine and wrong frequency. Content analysis of the incident reports described as moderate/severe harm or death found that administration incidents involving PN were often related to the wrong rate. *Rate* is not specifically listed as a medication error category option within the "database name removed" leaving reporters having to decide between wrong dose, quantity, strength or frequency. Cross-tabulation between medication process and medication error category showed for both administration and dispensing, omitted medication was the highest reported error category. In comparison, Storey et al.,[29] reported improper dose/quantity as the most common error in the administration process, and omission as the most common error in the dispensing process. In the "database name removed" database wrong quantity and wrong dose are listed as two separate error categories. If the results within the administration process for these two categories were combined, the total (n=243/1126, 22%) would exceed omitted medication, agreeing the above findings by Storey et al.,[29] that an incorrect dose or quantity was the most frequent error category for administration incident reports for PN in "Country Y" and "Country Z".

In this evaluation, quantitative analysis provided limited insight into PN components as contributory factors. The complexity of PN and its ingredients are not captured within this data. Content analysis of the free-text

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fields provided a more granular insight and revealed that specific ingredients such as intravenous ILEs, amino acids, electrolytes, glucose and micronutrients were involved in PN-related incident reports. This resembles the findings from previously discussed case reports and prevalence studies. [17,23,27,29,31,32,46-48] Inadvertently administrating ILE at the rate of the non-lipid PN, and vice versa, in neonates and infants was a common incident type seen in our study and literature.[27,31,46,48] Other incident reports such as missing ingredients from PN, using the wrong venous access and extravasation were also seen in our study and the literature. We didn't see the varied severe outcomes as reported in the case reports, but these are published to highlight fatal/rare outcomes.

An increase in the use of HPN has been reported in the "Country X".[49] This can be contributed to an increase in cancer patients starting HPN to improve quality of life by preventing the consequences of malnutrition.[49,50] A large number of incident reports involving HPN were related to a recent national incident. In 2019 there was disruption in HPN supply in "Country Y" and "Country Z" affecting over 500 patients.[51] Content analysis of incident reports described as moderate/severe harm and death in our study revealed this as a possible contributory factor. Some patients on HPN who experienced incidents were admitted to hospital for treatment, particularly when other co-morbidities were present. This suggested that organizational failures, such as missed/delayed deliveries, when combined with high-risk groups such as those dependent of HPN, can have disastrous effects. National incidents may be difficult to anticipate, however by highlighting high-risk patients, harm could be minimised. A recent evaluation by a HPN multidisciplinary team demonstrated interventions were recommended during 59.4% of follow-up assessments, and imperative to the ongoing care of these complex patients.[52] Murphy et al.[53] reported a case series of seven HPN incidents caused by formulation mistakes, leading to hospitalization of one patient. Human error was the primary cause, and they proposed prevention strategies such as integrated computerised systems, double-checking procedures and open communication. There are limited publications regards patient safety incidents related to HPN in the literature, and more are urgently required to understand risks, particularly in patients who are solely dependent on HPN for their nutrients, fluid and electrolytes.

4.2. Strengths and limitations

The main strength of this study is its originality and scale. The "database name removed" database has been used to evaluate medication incident reports, but not focussed on PN.[54,55] This study also includes all patient

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age groups, a time period sufficient to capture all relevant incident types, and an extensive search strategy to capture as many PN-related incident reports as possible.

The limitations of this study are that only a sample of the low and no-harm incident reports were available for analysis. We had to assume the sample we analyzed was representative of all PN-related incident reports. Also, we did not analyze PN-related patient safety incident reports in non-medication incident categories. Our data extraction process revealed that these incidents were reported in categories such as treatment/procedure, however their analysis was not feasible for this Master's study. Therefore PN incidents reported are likely to be an under-representation of the total number.

Drug searches of the "database name removed" system are conducted as free-form text using both generic and brand names of medicines. This creates the need for extensive data cleaning due to the risk of incorrect entries, and has previously been criticised by Cousins et al.[56] They suggested that medication names for all incidents should be selected from a national database of medicines, such as the "organization removed" Drugs and Devices list.[57] However, in the case of PN this is further complicated by the numerous components contained in one bag, being mistaken for a food product by some healthcare professionals and not being classified by the "organization removed" Drugs and Devices list.[57,58]

The use of voluntary reporting methods from a local or national database to capture patient safety incidents presents as a challenge as investigators have minimal control over the data reported. There is potential reporter bias in the form of missing data, under-reporting and subjectivity on applying scales for level of harm.[59] We have seen some of these issues in our study, where incident reports have been wrongly categorized, data are missing or categorized as *other* for certain fields. We planned to analyze staff reporter type however this field was rarely completed. Nevertheless, the data remains valuable in highlighting medication incident reports and guiding the development of future research.[54,60-62] Content analysis of free-text data within the incident reports has shown to provide more meaningful results, and should be adopted for future studies.

4.3. Recommendations

The future for minimizing patient safety incidents related to PN should be focussed on adding systems/processes in the workplace to reduce risks. The low number of incident reports related to

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moderate/severe harm or death is reassuring. 'Near misses' are incidents that have the potential to cause harm but were prevented. These are not separately captured by the "database name removed" and could be reported within the several thousand no/low harm incident reports. This study has provided an insight into PN-related incidents and contributory factors for moderate/severe harm incidents and deaths. A similar review of the no/low harm incidents could give an equally valuable insight and include near misses.

Administration was highlighted as the process with the highest number of incident reports, in all age groups and all degrees of harm. Contributing factors such as young age, mistakes and venous access devices were highlighted. These factors highlight the need for staff education and review of local standards/policies. Drug-error reduction systems (DERS) and 'smart' infusion pumps have been introduced in healthcare to help reduce drug errors by imposing dosing limits utilizing built-in built-in drug libraries.[63] They aim to remove the element of human error when setting up infusion pumps. Studies have demonstrated a reduction in programming error rates but with the introduction of new error types e.g., overriding pump warnings and out-dated drug libraries.[63-67] A recent "organization removed"-funded review of infusion devices recommended that advisory boards of relevant multi-professional organizations should develop validated national drug libraries for smart infusion pumps.[68] This could be a positive step in the development of smart pumps and their role in reducing programming errors for PN infusions.

The medication error categories seen in the dispensing process were omitted medication and wrong quantity, some of which were related to transcribing errors. Several studies have investigated the impact of computerized prescription tools on reducing errors related to PN, and this has been widely publicised in the USA.[6,69] In the "Country X" the uptake of electronic systems for prescribing medications such as intravenous fluids and PN is low.[70] This is likely due to limitations of prescribing systems to include variations in infusion rates, duration and volume for the range of intravenous infusions. The most effective tools have been demonstrated to be those with integrated prescribing and compounding features as they remove the transcribing process.[71-75] A national drive for quality improvement projects supporting integrated computerised systems suitable for PN should be considered.

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5. Conclusion

To our knowledge this study is the first national evaluation of PN-related incident reports in “Country Y” and “Country Z”. Consistent with previous non-“Country X”/local studies we demonstrated a low frequency of incident reports related to moderate or severe harm or death, that neonates are more susceptible to PN-related incidents and that incidents commonly occur during the administration process. We support the classification of PN as a high-risk medication, particularly in neonates and infants. Robust operational systems, including computerized tools should be introduced where possible to reduce errors. Patients dependent on HPN were identified as a high-risk group, requiring hospitalization, and reported a higher-than-expected degree of harm. Further investigations in this patient group are necessary. Near-miss incidents were not identified in this evaluation and content analysis of no/low harm incident reports may provide further insight. Limitations of voluntary reporting systems were recognized but the database was valued for the purpose of this study.

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Tables

Table 1. Patient characteristics of all PN-related incident reports by reported harm

	Frequency of incident reports within each reported degree of harm¶					
	No harm	**Low**	**Moderate**	**Severe**	**Death**	**Total (%)**
Patient age¶						
<28 days	495	62	10	2	1	570 (25)
1 month- 1 yr.	344	45	8	0	0	397 (18)
2-4 yrs.	60	8	0	0	0	68 (3)
5-11 yrs.	90	11	2	0	0	103 (5)
12-17 yrs.	51	5	1	0	1	58 (3)
18-25 yrs.	19	8	1	0	0	28 (1)
26-35 yrs.	30	9	1	1	0	41 (2)
36-45 yrs.	43	12	0	0	1	56 (2)
46-55 yrs.	85	20	1	0	0	106 (5)
56-65 yrs.	101	32	9	0	0	142 (6)
66-75 yrs.	146	26	4	0	0	176 (8)
76-85 yrs.	110	26	3	0	0	139 (6)
>85 yrs.	27	10	2	0	0	39 (2)
Total *(missing data for 319 entries)*	**1601**	**274**	**42**	**3**	**3**	**1923 (100)**
Location¶						
Inpatient	1507	242	28	2	1	1780 (79)
Support services	222	35	6	0	1	264 (12)
Other	110	19	3	0	0	132 (6)
General areas	25	4	2	0	0	31 (1)
Private house/flat etc	5	6	6	1	1	19 (1)
Day case services	3	1	0	0	0	4 (0)
Outpatient dept	2	2	0	0	0	4 (0)
Accident, minor injuries, medical assessment unit	0	0	1	0	0	1 (0)
In vehicle/in transit	1	0	0	0	0	1 (0)
Total *(missing data for 6 entries)*	**1875**	**309**	**46**	**3**	**3**	**2236 (100)**
Speciality¶						
Medical specialities	643	83	12	3	2	743 (33)
Other Specialities	354	53	9	0	0	416 (19)
Surgical specialities	259	70	11	1	1	342 (15)
Other	286	41	6	0	0	333 (15)
Children's specialities	177	26	7	0	0	210 (9)
Anaesthesia, Pain, Critical Care	64	14	1	0	0	79 (4)
Not applicable	39	11	0	0	0	50 (2)
Obstetrics & Gynaecology	23	8	0	0	0	31 (1)
Diagnostic Services	12	0	0	0	0	12 (1)
Unknown	9	2	0	0	0	11 (0)
Learning disabilities	8	0	1	0	0	9 (0)
Primary Care/Community	3	1	0	0	0	4 (0)
Accident & Emergency	2	0	0	0	0	2 (0)
Total	**1879**	**309**	**47**	**4**	**3**	**2242 (100)**

Note: ¶sub-categories as set within "database name removed" database

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Table 2. Medication incident characteristics of all PN-related incident reports by reported harm

Medication Process¶	Frequency of incident reports within each reported degree of harm¶					
	No harm	Low	Moderate	Severe	Death	Total (%)
Administration/Preparation in Clinical Area	914	184	22	4	2	1126 (50)
Preparation from all locations/Dispensing from Pharmacy	433	54	6	0	0	493 (22)
Prescribing	273	27	4	0	1	305 (14)
Other	184	29	9	0	0	222 (10)
Monitoring	63	14	4	0	0	81 (4)
Supply or use of OTC medicines	7	1	1	0	0	9 (0)
Advice	5	0	1	0	0	6 (0)
Total	**1879**	**309**	**47**	**4**	**3**	**2242 (100)**
Medication Error Category¶						
Other	497	73	20	0	1	591 (26)
Omitted medication/ingredient	212	65	11	2	1	291 (13)
Wrong quantity	183	29	1	0	1	214 (10)
Wrong/unclear dose or strength	175	25	4	1	0	205 (9)
Wrong drug/medicine	155	11	0	0	0	166 (7)
Wrong frequency	113	23	1	0	0	137 (6)
Wrong method of preparation/supply	96	17	0	0	0	113 (5)
Wrong/omitted/passed expiry	87	8	0	0	0	95 (4)
Wrong formulation	81	7	2	0	0	90 (4)
Wrong/ transposed/omitted medicine label	72	8	0	0	0	80 (4)
Wrong route	54	13	2	0	0	69 (3)
Mismatching between patient and medicine	62	6	1	0	0	69 (3)
Unknown	33	6	1	0	0	40 (2)
Wrong Storage	26	4	0	0	0	30 (1)
ADR- with use as intended	2	14	3	1	0	20 (1)
Contraindication in relation to drug/ condition	18	0	1	0	0	19 (1)
Wrong/omitted verbal patient directions	7	0	0	0	0	7 (0)
Wrong/omitted PIL	4	0	0	0	0	4 (0)
Patient allergic to treatment	2	0	0	0	0	2 (0)
Total	**1879**	**309**	**47**	**4**	**3**	**2242 (100)**

Note: ¶sub-categories as set within "database name removed" database
Abbreviations: ADR: adverse drug reaction; OTC: over-the-counter; PIL: patient information leaflet

For Peer Review

Table 3. Frequency of PN-related incident reports in each age group by medication process

Medication process¶	Frequency of incident reports in each age group (%)		
	Children (0-17 yrs.)	**Adults (≥18 yrs.)**	**Total**
Administration/Preparation in Clinical Area	623 (52)	379 (52)	1002 (52)
Preparation from all locations/Dispensing from Pharmacy	221 (18)	180 (25)	401 (21)
Prescribing	180 (15)	83 (11)	263 (14)
Other	110 (9)	62 (9)	172 (9)
Monitoring	59 (5)	13 (2)	72 (4)
Supply or use of OTC medicines	1 (0)	6 (1)	7 (0)
Advice	3 (0)	3 (0)	6 (0)
Total	**1197 (100)**	**726 (100)**	**1923* (100)**

Note: ¶sub-categories as set within "database name removed" database;*missing data for 319 entries*

Abbreviations: OTC: over-the-counter

For Peer Review

Table 4. Frequency of PN-related incident reports in each medication process by medication error category

Medication Error Category¶	Frequency of incident reports in each medication process¶ (%)							
	Prescribing	Preparation from all locations/ Dispensing from Pharmacy	Supply or use of OTC medicines	Administration/ Preparation in Clinical Area	Monitoring	Advice	Other	Total
Other	63 (21)	98 (20)	3 (33)	257 (23)	30 (37)	5 (83)	135 (61)	591 (26)
Omitted medication/ingredient	25 (8)	96 (19)	3 (33)	142 (13)	5 (6)	0 (0)	20 (9)	291 (13)
Wrong quantity	38 (12)	17 (3)	0 (0)	137 (12)	8 (10)	0 (0)	14 (6)	214 (10)
Wrong/unclear dose or strength	67 (22)	28 (6)	0 (0)	106 (9)	2 (2)	1 (17)	1 (0)	205 (9)
Wrong drug/medicine	33 (11)	38 (8)	0 (0)	89 (8)	1 (1)	0 (0)	5 (2)	166 (7)
Wrong frequency	21 (7)	3 (1)	0 (0)	104 (9)	6 (7)	0 (0)	3 (1)	137 (6)
Wrong method of preparation/supply	8 (3)	43 (9)	1 (11)	52 (5)	3 (4)	0 (0)	6 (3)	113 (5)
Wrong/omitted/passed expiry	2 (1)	21 (4)	0 (0)	52 (5)	12 (15)	0 (0)	8 (4)	95 (4)
Wrong formulation	18 (6)	33 (7)	0 (0)	34 (3)	0 (0)	0 (0)	5 (2)	90 (4)
Wrong/transposed/omitted medicine label	2 (1)	69 (14)	0 (0)	9 (1)	0 (0)	0 (0)	0 (0)	80 (4)
Wrong route	7 (2)	2 (2)	0 (0)	55 (5)	2 (2)	0 (0)	3 (1)	69 (3)
Mismatching between patient and medicine	11 (4)	27 (5)	0 (0)	28 (2)	0 (0)	0 (0)	3 (1)	69 (3)
Unknown	5 (2)	6 (1)	2 (22)	14 (1)	5 (6)	0 (0)	8 (4)	40 (2)
Wrong Storage	0 (0)	5 (1)	0 (0)	17 (2)	1 (1)	0 (0)	7 (3)	30 (1)
ADR- with use as intended	1 (0)	0 (0)	0 (0)	15 (1)	4 (5)	0 (0)	0 (0)	20 (1)
Contraindication in relation to drug/condition	3 (1)	4 (1)	0 (0)	10 (1)	1 (1)	0 (0)	1 (0)	19 (1)
Wrong/Omitted verbal patient directions	1 (0)	1 (0)	0 (0)	4 (0)	0 (0)	0 (0)	1 (0)	7 (0)
Wrong/omitted PIL	0 (0)	2 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	4 (0)
Patient allergic to treatment	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	2 (0)
Total	**305 (100)**	**493 (100)**	**9 (100)**	**1126 (100)**	**81 (100)**	**6 (100)**	**222 (100)**	**2242 (100)**

Note: ¶sub-categories as set within "database name removed" database

Abbreviations: ADR: adverse drug reaction; OTC: over-the-counter; PIL: patient information leaflet

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Table 5. Frequency of incidents type described in the free-text for moderate/severe harm and death incident reports

Incidents- themes and codes	Frequency	%
1. Clinical treatment decision-making error	**2**	**4%**
2. Medication not commenced in a timely fashion	**1**	**2%**
3. Medication unavailable- parenteral nutrition	**3**	**6%**
4. Prescribing medication incident	**4**	**8%**
4.1 Medication not prescribed	*1*	*2%*
4.2 Wrong strength	*1*	*2%*
4.3 Inappropriately prescribed/not stopped (insulin)	*1*	*2%*
4.4 Unsafe medication prescribed	*1*	*2%*
5. Dispensing/compounding/delivery medication incident	**16**	**30%**
5.1 Inappropriate medication	*2*	*4%*
5.2 Medication not delivered	*4*	*8%*
5.3 Medication damaged	*1*	*2%*
5.4 Wrong formulation	*3*	*6%*
5.5 Medication not dispensed	*6*	*11%*
6. Administering medications incident	**24**	**45%**
6.1 Wrong dose administered	*8*	*15%*
6.2 Medication not administered	*2*	*4%*
6.3 Wrong route administered	*1*	*2%*
6.4 Adverse event from medication administration	*13*	*25%*
7. Monitoring medication incident	**2**	**4%**
7.1 Inappropriate interpretation of result leading to mis-dosing (insulin)	*1*	*2%*
7.2 Medication dose (insulin) not adjusted, when appropriate	*1*	*2%*
8. Incorrect medication storage	**1**	**2%**
Total	**53**	**100%**

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Table 6. Frequency of contributory factors described in the free-text for moderate/severe harm and death incident reports *(Note, some incident reports described more than one contributory factor)*

Contributory factors- themes and codes	Frequency	%
1. Patient factors (Total)	**(37**	**42%)**
1.1 Patient age		
1.1.1 Infant <1 year	11	12%
1.2 Behaviour of patients/family		
1.2.1 Patient did not follow healthcare professional advice	1	1%
1.3 Pathophysiological factors		
1.3.1 Drug interaction with parenteral nutrition	1	1%
1.3.2 Co-morbidity - the presence of one or more additional diseases	8	9%
1.3.3 Failed treatment- no venous access	1	1%
1.3.4 Patient dependent on home parenteral nutrition	14	16%
1.3.5 Having parenteral nutrition	1	1%
2. Staff factors (Total)	**(14**	**16%)**
2.1 Task-a piece of work to be done or undertaken.		
2.1.1 Failure to follow protocol, procedures or regulation	2	2%
2.1.2 Inadequate skill set/knowledge	1	1%
2.1.3 Task not carried out/incomplete/inadequate	2	2%
2.2 Cognitive factors		
2.2.1 Mistake	9	10%
3. Equipment (Total)	**(10**	**11%)**
3.1 Lack of stock- parenteral nutrition	3	3%
3.2 Infusion pump device		
3.2.1 Pump unavailable	1	1%
3.2.2 Pump failure	1	1%
3.3 Venous access device		
3.3.1 Three-way tap	1	1%
3.3.2 Related to device used	4	4%
4. Organization (Total)	**(28**	**31%)**
4.1 Working conditions		
4.1.1 Staffing levels- provision of healthcare staff	1	1%
4.2 Protocols/Policies/Standards/Guidelines inadequate, absent or not available		
4.2.1 Procurement procedures	2	2%
4.2.2 Dispensing protocols inadequate/inefficient	2	2%
4.2.3 Infection control protocol	1	1%
4.3 External company/manufacturer		
4.3.1 Service failure due to miscommunication	2	2%
4.3.2 Service failure due to finance issue	1	1%
4.3.3 Service failure due to national incident	9	10%
4.3.4 Service failure due to internal error	2	2%
4.4 Continuity of care between different providers		
4.4.1 Locum/agency staff	3	3%
4.5 Education & Training		
4.5.1 Knowledge of others' roles	1	1%
4.5.2 Other training needs identified	2	2%
4.6 Service Unavailable		
4.6.1 Lack of/insufficient compounding facilities	2	2%
Total	**89**	**100%**

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Figures

Figure 1. Screening process of PN-related incident reports from the “database name removed” database

Figure 2. Breakdown of all PN-related incident reports by patient age groups

Figure 3. Diagram displaying outcomes of incident reports related to moderate/severe harm or death from the content analysis. *(Note, some incident reports described more than one outcome)*

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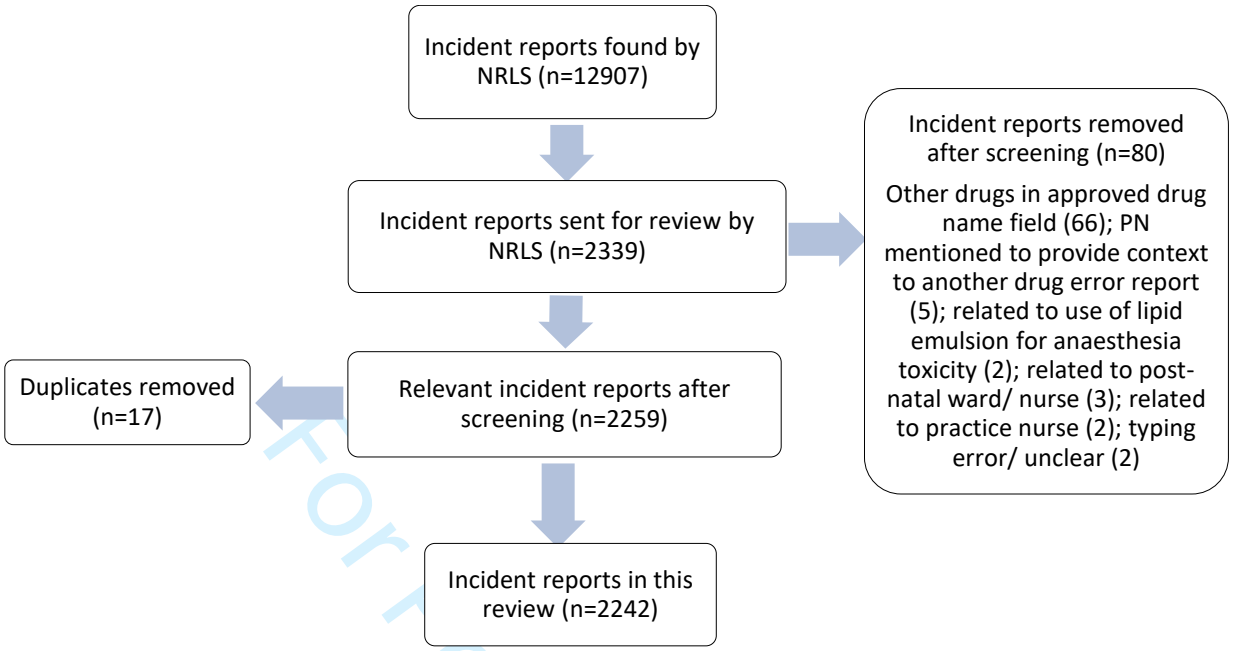

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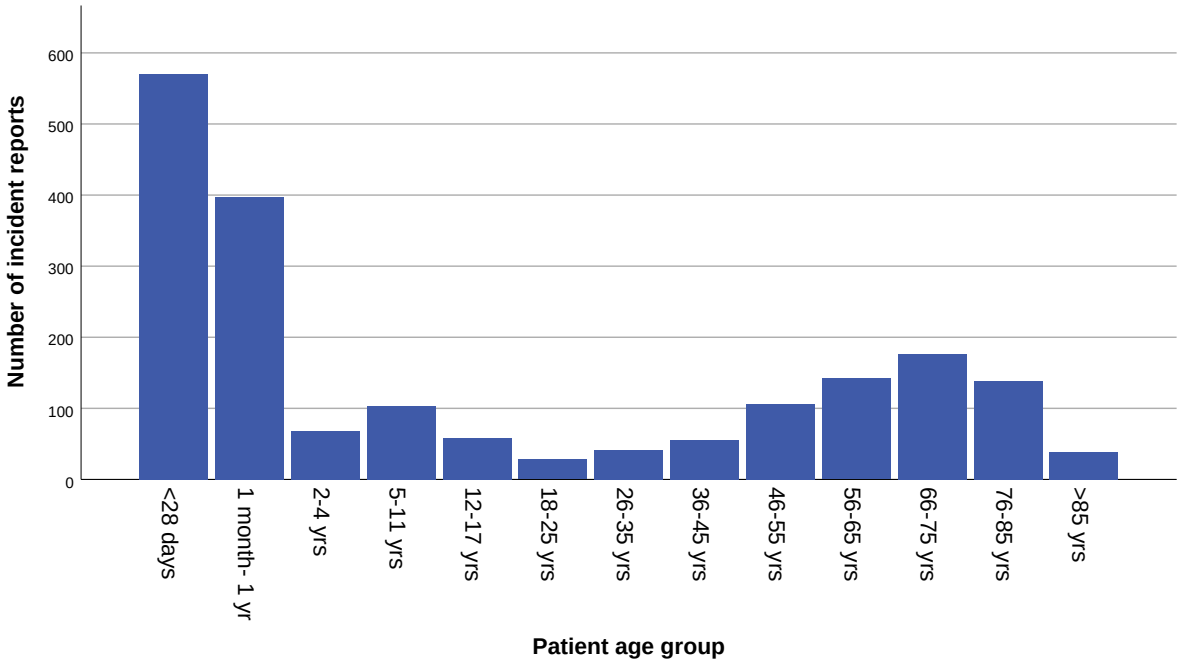
Number of incident reports
600
500
400
300
200
100
0
<28 days
1 month- 1 yr
2-4 yrs
5-11 yrs
12-17 yrs
18-25 yrs
26-35 yrs
36-45 yrs
46-55 yrs
56-65 yrs
66-75 yrs
76-85 yrs
>85 yrs
Patient age group

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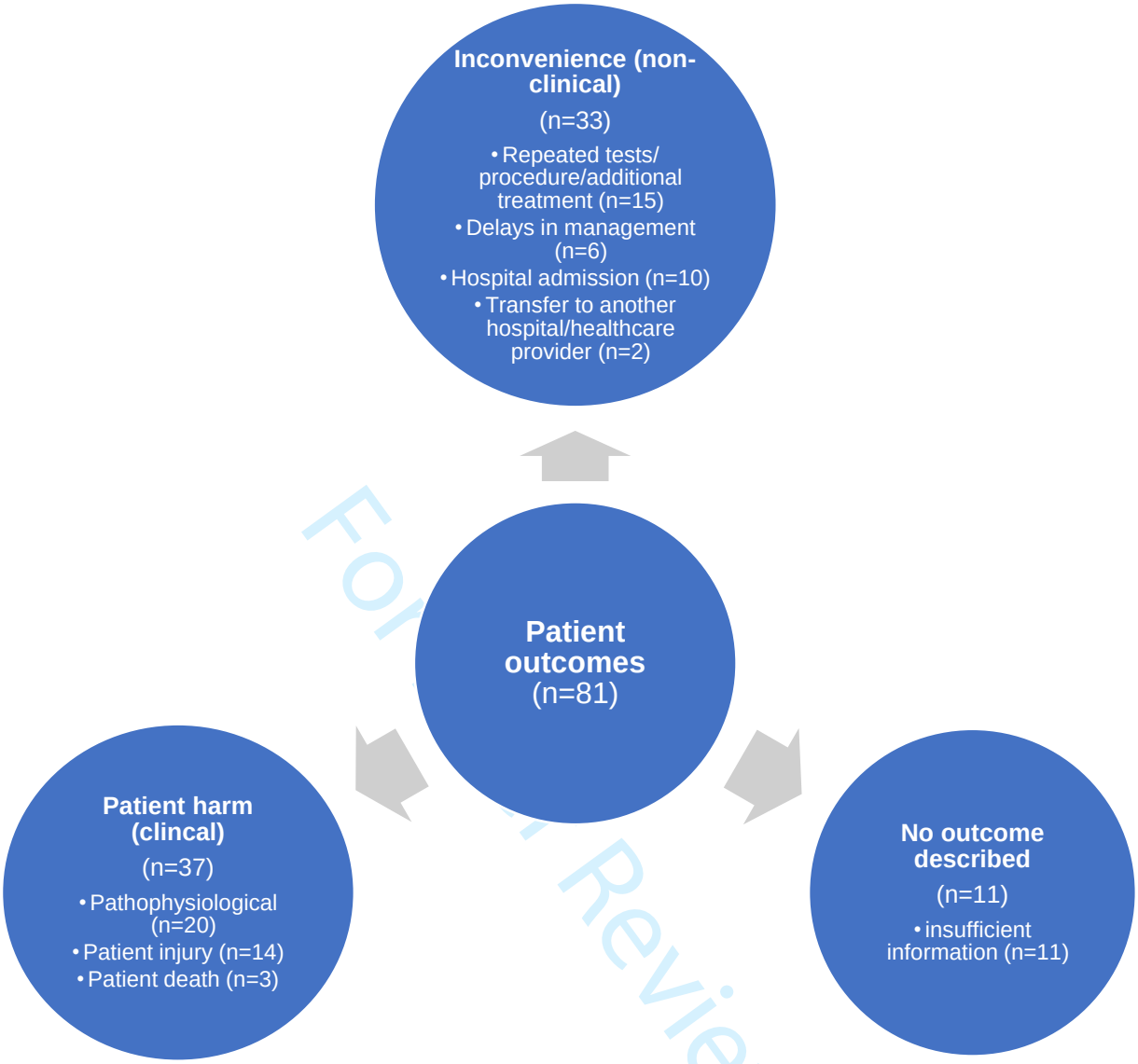

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Supplementary material

Table S1. NRLS Search Strategy and Sampling Method

Date Range:	Incidents reported to have occurred between 01 April 2015 and 31 March 2020 and reported to the NRLS on or before 16 April 2021.
Categorical Criteria:	Type of Incident IS EQUAL TO: Medication
Free-text filters:	**All terms searched in the following fields:**

A. BROAD NAME SEARCH:

1. Description of what happened
2. Actions Preventing Reoccurrence
3. Apparent Causes
4. Location - Free-text
5. Approved Drug Name (Drug 1)
6. Approved Drug Name (Drug 2)

B. BRAND NAME SEARCH:

1. Description of what happened
2. Actions Preventing Reoccurrence
3. Apparent Causes
4. Approved Drug Name (Drug 1)
5. Approved Drug Name (Drug 2)

A. Free-text *BROAD NAME* search terms based the following terms (including misspellings and variations):

Free-text Search:	PN OR HPN OR TPN OR parenteral nutrition

B. Free-text *BRAND NAME* search terms based the following terms (including misspellings and variations, all separated by 'OR'):

Aminolect	Intralipid	Omegaven
Aminomix	Kabiven	Primene
Aminoplasmal	Lipodem	SMOFkabiven
Aminoven	Lipoflex	SMOFlipid
Babiven	Lipofundin	SMOFven
Clinimix	Numeta	Synthamin
ClinOleic	Nutriflex	Triomel
Finomel	Omeflex	Vamin
		Vitrimix

Sampling: Dataset provided by NRLS included *all* output from search "**A *AND* B**", and a random sample of output from search "**A *OR* B**". *All* incidents resulting in moderate/severe harm or death from both searches were supplied.

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Table S2. NRLS fields used in data analysis

	In this study fields used in…	
Data field	Quantitative analysis	Content analysis
incident ID	no	no
Care Setting of Occurrence	yes	no
Location (lvl1)	no	no
Location (lvl2)	yes	no
Location (lvl3)	no	no
Location - Free-text	no	no
Incident Category - Lvl1	no	no
Incident Category - Lvl2	no	no
Incident Category - Free-text	no	no
Description of what happened	no	yes
Actions Preventing Reoccurrence	no	yes
Apparent Causes	no	yes
Patient Age Range	yes	no
Specialty - Lvl 1	yes	no
Specialty - Lvl 2	no	no
Speciality - Free-text	no	no
Reported Degree of Harm	yes	no
Med Process	yes	no
Med Error Category	yes	no
Approved Name (Drug 1)	no	no
Proprietary Name (Drug 1)	no	no
Route (Drug 1)	no	no
Type of Device	no	no
Date incident received by NRLS	no	no
Current location of device	no	no
Device name	no	no
Manufacturer	no	no
Supplier	no	no
Approved Name (Drug 2)	no	no
Proprietary Name (Drug 2)	no	no
Year of Occurrence	yes	no
Month of Occurrence	no	no
Type of device - free-text	no	no
termfound	no	no
TriggerCode_Found_In	no	no
Staff Reporter type	yes	no

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