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Accuracy of Intravenous and Enteral Preparations Involving Small Volumes for Paediatric Use: A Review.

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Abstract

Background: Children often need to be administered very small volumes of medicines that are authorised for use in adults. Neonatal drug delivery is particularly challenging and doses are often immeasurable with the equipment currently available.

Aim: To summarise research to date on the accuracy of intravenous and enteral medicine preparation requiring small volumes (<0.1mL), with a focus on paediatric use and to identify areas for further work.

Method: Twenty-three publications were identified for the narrative review via: Web of Science (1950-2016), Cumulative Index to Nursing and Allied Health Literature (1976-2016), Excerpta Medica Database (1974-2016) and International Pharmaceutical Abstracts (1970-2016) searches. Nine additional papers were identified through backward citation tracking and a further 17 were included from the personal knowledge of the review team.

Results: Measurement of volumes (<0.1mL), for enteral and intravenous dosing, account for 25% of medicine manipulations within paediatric hospitals. Inaccuracies are described throughout the literature with dose administration errors attributed to technique, calculation, dilution and problems associated with equipment. Whilst standardised concentrations for intravenous infusion and drug concentrations which avoid measurement of small volumes would ameliorate problems, further work is needed to establish accurate methods for handling small volumes during the administration of medicines to children and risk minimisation strategies to support staff involved are also necessary.

Conclusion: This review has revealed a paucity of information on the clinical outcomes from problems in measuring small volumes for children and highlighted the need for further work to eliminate this source of inaccurate dosing and potential for medication error.

Introduction and background to paediatric medicine

Children have historically been referred to as "therapeutic orphans"(1) suggesting that they were traditionally overlooked within research into disease and pharmacological treatment. This has considerably limited the numbers of licensed or authorised medicines available for children (2). In healthcare, the term 'children' is often used as an umbrella term for all sub-groups of paediatric patients and can cover preterm babies weighing 500g to adolescents weighing 100 kg. The physiological and pharmacological disparity between them is profound, creating further challenges in developing suitable drug therapy in this area (3).

Newer legislation, such as the European Union's Paediatric Regulation, has been put in place as the growing need for the development and authorisation of children's medicines has been recognised (4). A report by the European Commission stated that as a result of the regulation, paediatric medicine has become an integral part of medicine development with over 600 paediatric investigation plans (PIPs) being agreed from 2007 – 2012 (4). The effect on drug development remains to be seen due to the lengthy nature of trials and legalities surrounding marketing authorisation. Neonates are the most neglected group in this population as only 30% of current PIPs include them (4).

The lack of commercially available age-appropriate formulations makes it difficult to administer medicines to children accurately (5). Doses required for children can vary 100-fold throughout childhood. Consequently, proportions of the marketed dosage forms are required to allow an appropriate paediatric dose to be given by manipulation, often with a medicine being used off-label (6, 7). Examples of manipulation include additional dilution of an injection to allow the required volume to be measured accurately or to provide an accurate rate of infusion. Manipulation occurs frequently in specialist and high dependency care and research has shown that this often leads to errors (8).

Previously, 12.3% of prescribed doses of liquid medicines (for oral and intravenous use) on neonatal intensive care units (NICU) and other children's wards were reported as being immeasurable with the available dosage forms (9). Additionally, only 35% of prescriptions issued on NICU use formulations in a licensed way; a figure far less than in other areas of paediatric medicine (10-12) despite advances made towards innovative drug formulations for paediatric patients (4). An important consequence of this is that healthcare professionals are often required to give children very small volumes of medicines that are licensed for use in adults (13-15). Intravenous delivery is the most widely used method of medicine administration in very ill preterm and term neonates and children (16).

Children are exposed to potential adverse drug events up to three times more frequently than adult in-patients and it is estimated that up to 54% of these errors involve intravenous medicines (17). In high dependency units, such as NICU, 91% of admissions were associated with a medication error, compared to 50% of neonatal admissions to other wards (17). Medication error rates vary widely between studies, depending on settings and methods involved. In a review of eleven studies, Chedoe et al (18) identified that the highest rate at which medication errors occur in NICU was 5.5 errors per 100 prescriptions. Prescribing and administration errors, across five different hospitals in London, were reported on average as 13.2% and 19.1% respectively and administration errors most commonly originated from medicine preparation errors (19). Patients in this setting are at a greater risk due to the small volumes often required; an error that may only seem slight to the naked eye but could represent a ten-fold error or more, a scenario unlikely to occur in the adult setting (20).

Where children and medication errors are concerned, higher risk is associated with increased vulnerability to adverse effects. This risk is due to a number of factors: inability to communicate effectively; a higher prevalence of rare diseases in childhood, thus creating a lack of clinical experience in treatment; constant physical and psychological changes over time, including intra-individual and inter-individual variation in drug metabolism during growth and development; small medicine doses often involving decimal points, thus giving opportunity for

significant degrees of error; and errors in prescription writing due to the lack of appropriate formulations (21-23). The need to reduce medication errors and improve patient safety in this area is clear.

Methods

Search strategy

Searches were undertaken using four databases: Web of Science (1950-2016), Cumulative Index to Nursing and Allied Health Literature (1976-2016), International Pharmaceutical Abstracts (1970-2016) and Excerpta Medica Database (1974-2016). Limits were applied to the Web of Science search (see Appendix A). An adaptive search strategy, based on one developed for a previous review was used (24). The search strategy is presented in Appendix B. Following the selection of publications for inclusion, backward citation tracking was undertaken for each paper if it was indexed in SCOPUS. Additional relevant publications were highlighted for inclusion by members of the review team.

Selection of papers for inclusion

Titles and abstracts were screened by one reviewer (LPA). Three experts in the field of paediatric and neonatal formulation research (AJN, MAT & JLF) reviewed the titles selected to confirm that they were suitable for inclusion and to recommend the inclusion of any additional literature known to them. Publications were included in this review if they related to the accuracy of intravenous and enteral medicine preparation for children and/or involved small volumes (<0.1mL).

Results

Search results Database searches identified 5948 unique references of which 23 (13, 15, 19, 25-44) were selected. A further nine references were identified through backward citation tracking (14, 45-52) and 17 were highlighted by the review team (5-9, 53-64) (Appendix C).

Narrative Review

Manipulation of medicines for intravenous and enteral use - small volumes

Recent studies have investigated the practice of manipulating medicines in order to provide accurate doses for children, in particular the requirement to dilute very small volumes (<0.5mL) (13-15). One study identified that the measurement of volumes of <0.1mL, for both enteral and intravenous dosing, account for a quarter of medicine manipulations within paediatric and neonatal hospital settings. Frequently, these volumes are required for intravenous administration (15) . Isaac et al (35) found that 25% of patients on paediatric intensive care units (PICU) were prescribed a medicine that required a small volume measurement of ≤0.2mL, with the intravenous route accounting for 80% of the drug delivery methods. Uppal et al (14) provide further support, stating that 7.4% of intravenous doses require preparation with <0.1mL of stock solution. It was concluded that this is necessary for the paediatric use of a wide range of narcotics and immuno-suppressants in Canada (14) with captopril, morphine, furosemide and ranitidine the most commonly found in the UK (35).

Small volume measurement and preparation for administration often involves the administrator using relevant calculations, along with dilution and subsequent mixing with compatible diluents thereby introducing a potential for errors to occur. A number of publications suggest that a high incidence of imprecision and dilution errors occur in the preparation of intravenous medicines and the preparation of small volumes of medicines is inaccurate (13, 26, 41, 56).

What is our current understanding about the accuracy of prepared intravenous medicines?

Morphine infusions prepared for a NICU in a UK hospital showed concentration deviations outside of the British Pharmacopoeia limit set for morphine sulphate injection (a maximum of ± 7.5% from the labelled concentration) (26). 19.2% of infusions were outside of the limit when prepared by nurses on the ward and 7.8% were outside this limit when made within a pharmacy-run intravenous preparation service. 93% of these "out of specification" results occurred when volumes of ≤1mL of morphine injection were required to prepare the infusions (26).

Furthermore, this problem was echoed in a direct observational study of a non-clinical environment in Canada, in which health care professionals prepared morphine sulphate infusions. Errors were detected at each and every stage of the preparation, and a significantly higher number was found when preparation required smaller dose volumes and the use of more concentrated solutions, i.e. where more dilution was required. For example; the use of 10mg/mL solution to produce a required concentration of 0.6mg/50mL required volume measurement of 0.06mL (13).

Studies in anaesthesiology, where the use of intravenous medicines is essential, indicated similar findings. Analyses of the content of unused syringes containing drugs regularly used in anaesthesiology (fentanyl, thiopental, lidocaine, atracurium) revealed that 29% showed drug concentrations outside the specified acceptability range and 4% contained more than twice the targeted drug concentration. Errors closely correlated with multiple dilutions of high strength formulations, and hence measurements of small volumes of initial drug solution, and these were seen particularly in preparations involving fentanyl (41). The complexity of preparation, often involving multiple calculations, was implicated in dilution error. High rates of imprecision were observed where serial dilution was required (41).

Campino *et al* (29) concluded that errors in precision were more common than calculation errors with regard to concentrations of tobramycin and vancomycin solutions administered on a regional NICU. Precision errors were defined as deviation between target concentration of solution and actual concentration determined in the laboratory by > ±10%. Calculation errors were defined as the deviations between prescribed dose and calculated dose by nurses that would theoretically be given by > ±10%. Occurrence rates were 37.9% and 4.6% respectively (29).

A high incidence of errors, which were defined as any deviation from the prescription or manufacturer's instructions during preparation or administration, was observed during intravenous medicine preparation and administration in German and UK teaching and non-teaching hospitals (48% and 49% respectively). Most of these errors were associated with multiple step preparations (42, 61); very small volumes and the use of unfamiliar preparations were later identified as contributing reasons for errors within multiple step preparations (43).

Discrepancies were found between ordered and delivered concentrations of opiates in neonatal and paediatric critical care in Canada (39). Two thirds of infusions were outside of the accepted limits of variation for the study (defined as ≤10% from the ordered concentration in line with US and Canadian pharmaceutical preparations), with 6% of infusions having a two-fold higher concentration than ordered. The inconsistencies ranged from -78% to +210% from the desired concentration. Specifics regarding volume measurement were not stated (39).

A wide variation was ascribed, in part, between ordered and actual concentrations of preparations of dobutamine, dopamine and epinephrine in a paediatric intensive care unit, to a failure to account for salt components within some formulations. Such drugs are used in critically ill patients and variability in dosing could well contribute to haemodynamic instability (45). Differences between prescribed and actual concentrations (ranging from 75.8% - 102.4% of the prescribed concentration) of vancomycin infusions were also documented after investigation on a paediatric and neonatal intensive care unit although possible reasons for discrepancies were not given (59).

The requirement for dilution of 'adult' vials in order to give paediatric doses has yielded errors in the region of 10-100 fold from the point of prescribing to administration (36, 53). Thirty one percent of prescriptions on a neonatal

unit required one-tenth of a ready-made vial, and 4.8% required less than one-hundredth (30). Thus, there is evidence that small volume measurements are often inconsistent. Our interpretation of this evidence is that healthcare faces a very real problem. Significant opportunities for catastrophic medicine administration errors exist; such errors would cause avoidable morbidity and mortality.

The preparation and administration stages involved in intravenous therapy involve the most error (55, 62). The ability of nurses to use calculations successfully in this process has been praised, with a call for further investigation into other phases involved in preparation and administration (62). Failure modes analysis supported this and five out of the top ten "critical failure modes" occurred within the preparation stage (55). A systematic review of where errors occur identified that reconstitution of drug and diluent was a significant area and the need for further work to establish the most efficient and accurate technique to produce correct preparations was identified (38).

Problems arising from equipment

Inaccuracies can also arise from the equipment used to prepare paediatric doses of intravenous medicines. The dead space within a syringe can contribute to overdosing. Dead space volume is the volume that remains in the syringe, within the hub and needle space, after the plunger is fully compressed, and could be inadvertently administered. For this reason it is vital that preparation technique is correct as it has been reported that doses as high as 4.5 times of those recommended can inadvertently be given. In the case of a drug with a narrow therapeutic index such as digoxin, this can result in potentially toxic levels (28, 44). Berman *et al* (54) noted variably high serum levels of digoxin in low birth weight infants given similar doses and that flushing the syringe after its contents were expelled resulted in more than twice the intended dose being administered to the infant as the dead space volume was administered.

Furthermore, an incident occurred which involved the administration of a bolus dose of metoclopramide that had been prepared using an incorrect technique. Metoclopramide was measured in the same syringe as subsequent sodium chloride volume measurement; consequently the dead space volume of metoclopramide was also administered to a neonate, resulting in a two to three times overdose (42).

Casella *et al* (46) reported unacceptably large errors when small volumes, for example 0.01mL, were measured using 0.3mL insulin syringes. Coefficient of variations tended to decrease as larger volumes were measured and mean errors as large as ±2% have been found in accuracy and reproducibility investigations, in some cases resulting in inaccuracies of at least one syringe division. With this said, this size of error can still be within standards set for syringes by The International Organization for Standardization (ISO) and, depending on the medicament, be considered as clinically irrelevant (48).

Dosing accuracy varies depending on the brand, size of syringe and the liquid measured. Investigating the accuracy and reproducibility of different types of syringe used to measure small volumes (0.05mL and 0.1mL) for intra-vitreal injection, variability was apparent with Nipro® TB syringes yielding the best accuracy (40). As a result, there has been a call for manufacturers to consider dosing volumes in relation to potential patient sizes, and to also provide guidance on optimum administration devices to use with reference to the pharmaceutical agent (34). The cumulative error of stages involved in the preparation of intravenous medicines is multiplicative and therefore could be as high as 38%, depending on what is considered acceptable. These data take into account vial concentration, calculation errors, forced rounding errors, volumetric errors of syringe and inaccuracies in dead space (65).

Impact of dosing inaccuracies

Investigation into the clinical impact of inaccuracies to date is limited. As an example, Parshuram et al (49) studied the impact of unanticipated variation in intravenous methotrexate dosing but failed to demonstrate a significant link between measured total methotrexate dose given and serum concentration or clinical toxicities.

Does place of preparation or health care professional performing the preparation have an effect on accuracy?

Errors are commonly found when infusions are prepared at the point of care (13, 26, 41, 52) and improvements are made when a centralised system for preparation is used (26, 47). However, both methods yield worrying deviations from the required stated concentrations.

The use of pre-filled syringes for infusions provides more efficient treatment in an emergency situation than preparation of the infusions at the bed side; a significant reduction in deviation from the expected concentration was also shown in one comparison (25). The same investigation confirmed that precision and accuracy vary depending on the healthcare professional preparing the pre-filled syringes; pharmacists are more accurate than physicians. Furthermore, a calmer environment for preparation yields increasing precision as demonstrated by those prepared in pharmacy and those sourced from the pharmaceutical industry (25). Previous studies indicated that nurses were less prone to error introduction in preparation tasks than anaesthetists, but more errors were introduced at the calculation stage by nurses than anaesthetists (32). Recently, no differences in the accuracy and precision of intra-vitreal dose preparation of 0.05mL using 1.0mL disposable syringes (57) were noted between nurses and physicians.

What practices are in place to reduce inaccuracies?

The UK National Patient Safety Agency (66) issued an alert acknowledging the risk associated with injectable medicines and recommended risk assessment for all injectables, although it has been argued that the developed tool did not specifically consider the issues faced when preparing intravenous medicines for children and neonates (67).

No specific guidance on how to manage issues of inaccuracies is available, so nursing staff have adopted crude methods such as carrying out dilution in a large syringe after initial measurement of medicine volume, (leaving the dead space volume within the initial syringe) (68), using insulin syringes with no dead space and including the dead space volume in the dose calculation (28).

Dead space volume must be considered if drawing up multiple medicines into the same syringe. If three medicines are drawn up sequentially a larger amount of the first two will be administered. When the second is drawn up the dead space volume of the first will be released from the hub and needle space into the graduated portion, to make way for the second, and the same with the volume of the second as the third is drawn up (63).

An investigation into the measurement of insulin using pen injectors (NovoPen® and BD Pen®) and syringes has shown that both device types are inaccurate at measuring 1 unit of insulin (100units/mL), with devices improving in accuracy with progressively larger volumes. This research did not use half unit pens that are now available. Syringes overdosed and Pen injectors consistently under dosed. Pen injectors were significantly more accurate than syringes but variability in dosing was similar for both (33). Subsequently improved accuracy of pre-filled insulin pens as opposed to vial and syringe methods has been demonstrated (58).Therefore pen injectors may be favourable; however, education is required if patients are transferred between different devices (33). Casella *et al* (46) concluded that the error introduced when measuring ≤2 units (100units/mL) is so large that dilution of insulin before measurement should be carried out where possible in an inpatient setting. Furthermore, the smallest syringe possible is often chosen to measure the required volume; this has been adapted as a technique and is supported by evidence (31, 48, 50, 51). In addition, Isaac et al (56) explored different methods of small volumes measurement of insulin and concluded that all showed inaccuracies; this included dilution and direct withdrawal with and without priming. For volumes of ≥0.05mL direct withdrawal may be more accurate, but dilution methods show better reproducibility.

The implementation of standardised concentrations of intravenous infusions for paediatrics may reduce common inaccuracies and errors (13, 14, 26, 64). Implementation of standardised concentrations in conjunction with other interventions, such as use of ‘smart’ syringe pumps and re-labelling of infusions (formatting label information to

match pump programming) resulted in a significant reduction in error (37). Improved dosing precision was confirmed with a paediatric vial containing an age-appropriate concentration of amikacin in comparison to an adult vial, with a five-fold higher concentration (27). The concern over increased cost and confusion between different vial concentrations likely stands as a barrier to implementation for different products and hospitals worldwide.

The results of a survey demonstrating acceptability of proposed standard concentrations of 17 medicines, commonly given by infusion, amongst 164 critical care units (63% of UK NHS trusts) have been provided to the Intensive Care Society in the UK (69). Similar work was carried out in USA by the Institute for Safe Medicine Practices (70) as a result of numerous safety alerts (71, 72) and many institutions employ standardised concentrations. Seventeen standardised weight categories and corresponding doses for 74 primarily (86.5%) intravenous medicines were established for the neonatal population with an aim of reducing the problems associated with dose delivery in this area (60).

Summary

The requirement to measure small volumes, for both oral and intravenous use, occurs frequently in paediatric settings. There is a substantial source of error involved in all stages of preparation of doses involving the use of such volumes. The errors introduced translate into discrepancies between the concentrations of drugs that are prescribed and the concentrations that are administered. Much literature describes deviations in the concentration of opiates for infusion. This occurs whether medicine is prepared at ward or pharmacy level. Published research has concluded the requirement of paediatric standardised infusion concentrations, but it is questionable how realistic this is for all settings. Although pharmacy and industry sourced pre-filled syringes are used in some settings, it is not realistic for all scenarios. Further, it is highly unlikely that these devices would appear with appropriate dosing for paediatrics and thus manipulation prior to use would still be required. Further work is needed to establish the most accurate methods for handling small volumes during the administration of medicines to children. Risk minimisation strategies, such as specific training and additional information at the point of use to support staff involved are also necessary.

Conclusions

This review identifies the need to quantify the sources of error in preparation of intravenous and enteral medicines, namely techniques and equipment used, the effects that this may have on therapy, with an estimation of cost implications. Work should lead to recommendations which will inform industrial and clinical aspects of medicine preparation, in order to improve current practice and reduce these inaccuracies. It is hoped that this review of the extant data will pave the way for the future development of standardised concentrations of commonly used medicines in all settings including paediatrics. However, there will undoubtedly forever be a requirement for preparation and use of small volumes for drug delivery due to the wide range of dose and medicine requirements in paediatrics.

Appendix A – Limits applied to Web of Science Search

English Language

Exclude: MICROBIOLOGY OR SOCIAL ISSUES OR DEMOGRAPHY OR TRANSPLANATATION OR FOOD SCIENCE TECHNOLOGY OR CHEMISTRY OR MATERIALS SCIENCE OR SOCIOLOGY OR SPORT SCIENCES OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR SUBSTANCE ABUSE OR ANATOMY MORPHOLOGY OR OPTICS OR BIOCHEMISTRY MOLECULAR BIOLOGY OR REHABILITATION OR LEGAL MEDICIEN OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR COMPUTER SCIENCE OR AGRICULTURE OR FAMILY STUDIES OR SCIENCE TECHNOLOGY OTHER TOPICS OR SPECTROSCOPY OR REPRODUCTIVE BIOLOGY OR IMAGING SCIENCE PHOTOGRAPHIC TECHNOLOGY OR ACOUSTICS OR GENETICS HEREDITY OR PHYSICS OR SOCIAL SCIENCES OTHER TOPICS OR LINGUISTICS OR GOVERNMENT LAW OR PATHOLOGY OR CELL BIOLOGY OR BIOPHYSICS OR BEHAVIOURAL SCIENCES OR PARASITOLOGY OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAING OR INFORMATION SCIENCE LIBRARY SCIENCE OR TELECOMMUNICATIONS OR MEDICAL LABORATORY TECHNOLOGY OR SOCIAL WORK OR PHYSIOLOGY OR MEDICAL INFORMATICS OR AUTOMATION CONTROL SYSTEMS OR RESEARCH EXPERIMENTAL MEDICINE OR ZOOLOGY OR BUSINESS ECONOMICS OR URBAN STUDIES OR AUDIOLOGY SPEECH LANGUAGE PATHOLOGY OR NUCLEAR SCIENCE TECHNOLOGY OR ENVIRONMENTAL SCIENCES ECOLOGY OR ETHNIC STUDIES OR MATHEMATICS OR ANTHROPOLOGY OR METEOROLOGY ATMOSPHERIC SCIENCES OR LIFE SCIENCE BIOMEDICINE OTHER TOPICS OR PLANT SCIENCES OR MICROSCOPY OR NUTRITION DIETETICS OR MECHANICS OR ENGINEERING OR COMMUNICATION OR VIROLOGY OR THERMODYNAMICS OR ENERGY FUELS OR DEVELOPMENTAL BIOLOGY OR VETERINARY SCIENCES OR CRIMINOLOGY PENOLOGY OR EDUCATION EDUCATIONAL RESEARCH

Appendix B – Search Terms

1 Terms related to intravenous` route

inject* OR intravenous OR IV OR infusion* OR syringe*

2 Terms related to process

(small ADJ2 volume*) OR (low ADJ dos*) OR dilution* OR technique* OR manipulation* OR preparation

3 Terms related to accuracy and precision

accurac* OR inaccurac* OR precis* OR reproducib* OR accurate OR measur* OR variab*

4 Terms related to errors

error* OR overdose OR adverse drug event OR discrepanc* OR overadministration

5 Terms related to population

child* OR pediatric* OR paediatric* OR neonat* OR infant*

Combine as follows:

1 AND 4

1 AND 2 AND 3

1 AND 2 AND 4

1 AND 2 AND 5

1 AND 3 AND 4

1 AND 3 AND 5

1 AND 4 AND 5

2 AND 3 AND 4

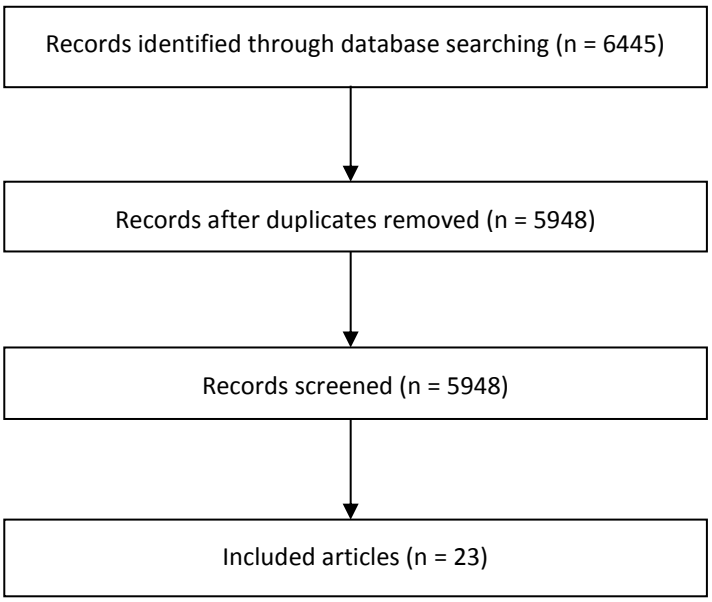
2 AND 3 AND 5

3 AND 4 AND 5

4 AND 5

Combine the above combinations with OR

Appendix C **Database Search Flow Diagram**



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