A NATIONAL CONSENSUS FOR PAEDIATRIC AND NEONATAL CARE
IN THE UNITED KINGDOM

FIXED CONCENTRATION INFUSIONS

On behalf of the Making it Safer Together Standardisation Working Group

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A National Consensus for Paediatric and Neonatal Care in the United Kingdom

FINAL REPORT

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Abstract

Background

Medication error is common in paediatric care and the causes of these errors are multi-factorial, including calculation error and manipulation inaccuracy. Weight-based infusions are the standard-of-care in the UK, requiring complex calculation and manipulation processes in order to administer these medicines to children and young people. These methods were developed over 40 years ago to enable administration using analogue systems.

Continuously infused medicines are associated with error and are often linked to patient harm due to their association with high-risk medicines. Bespoke solutions predispose patients to these risks, and are inherently inefficient. With sophisticated digital administration devices now used universally, it is difficult to justify continued use of patient specific infusions. NHS organisations are demanding increased efficiency within fixed resources, and the commitment to quality is irrefutable. It is no longer justifiable to continue the use of weight based solutions.

Methods

This project sought to define a consensus on medication concentrations for the twenty most commonly infused medicines in paediatric and neonatal care. The Delphi method was used, and a self-administered on-line survey was circulated to 1000 paediatric professionals (nurses, doctors and pharmacists) across the UK. The initial framework was developed using data derived from a scoping survey of paediatric and neonatal intensive care units undertaken in summer 2016.

The survey asked respondents to choose two concentrations from a pre-defined selection that would be suitable for use in six clinical scenarios. The threshold of consensus was set at 70% agreement over two concentrations. Those drugs and scenarios that did not achieve consensus after one cycle of the survey were resurveyed with adjusted concentrations where suitable. The final consensus framework was ratified at a professional consensus conference in February 2017. A third survey was necessary for morphine and dinoprostone in neonates, and clonidine in paediatrics as there was difficulty in achieving consensus. This survey was distributed to attendees of the conference only.

Results

1000 respondents were surveyed in each cycle of the survey and response rate was 6.5% and 5.3% respectively, however the respondents were representative of the sample. Attrition rates in each survey were high (74% and 68% in each cycle) which is reflective of the size and length of the survey. After Cycle I of the survey, consensus was achieved in 46.5% of scenarios across 70.8% of drugs (mostly older/heavier children.) After Cycle II of the survey this increased to 73.9% of scenarios and 95% of drugs. In the final survey 68 respondents were surveyed with 13 responses (response rate 19.1%) and consensus was achieved in 2/4 solutions. Morphine for pre-term infants and dinoprostone were removed from the final consensus framework.

Discussion

The proposed framework bears comparison with other frameworks from around the world, and also with published adult recommendations which supports the validity of this framework. The involvement of professionals and stakeholders in the development of this framework adds strength to the findings. However, this is just a conceptual model at present and requires additional study to identify the true utility of the recommendations in clinical practice. There were also legitimate concerns raised regarding the support that services and individuals will require to incorporate fixed concentration infusions in their practice, and how they should be presented in the future.

Conclusions

This report presents the first UK-wide consensus framework on infusions for use in paediatric and neonatal care. It is more robust than frameworks established by expert committees because it has directly involved clinicians, nurses and pharmacists in its development. A programme of research to explore the risks associated with FCIs and the barriers to implementation must be undertaken. Implementation must also be evaluated using controlled studies across a variety of care contexts.

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Introduction

Medication errors are estimated to contribute to 7500 excess deaths every year in the USA (1) and are associated with a cost to the UK National Health Service (NHS) of approximately £750m (2). In children these risks are even more pronounced. It is estimated that medication error in children occurs in approximately 19.4% of prescriptions (3). It has been claimed that continuously infused medicines represent a significant risk of error in paediatric practice (4) and have been associated with fatalities (5).

There are many reasons for this association between infused medicines and harm in children and young people, though there is commonality with the issues associated with other paediatric medications. The need to calculate doses on the basis of patient weight creates opportunity for calculation and manipulation error (6), the use of formulations and presentations designed for adults present errors associated with manipulation and selection (7) and a lack of appropriately studied and licensed formulations predisposes children to adverse drug events (8).

However, continuously infused medicines incorporate a large proportion of those medicines that are termed “high risk” or “high alert”(9) – opiates (morphine, fentanyl), catecholamines (adrenaline, dopamine) and anticoagulants (heparin) – that are disproportionately associated with patient harm. This is related to the intrinsic properties of these medications with a narrow therapeutic index, direct effect on respiratory or cardiovascular function and on their requirement for complex dosing calculations and monitoring. A substantial proportion of medication errors in paediatric intensive care (PICU) have been associated with these medicines (10).

There are a range of issues that directly affect the safety of continuously infused medicines in paediatric care and for which interventions are required to mitigate them. These are summarised over the coming paragraphs.

Accuracy

Infusions are prepared almost universally in the clinical area by nursing or medical staff. Paediatric infusions have historically been prepared using the "Rule of Six" (RoS) which is a mathematical formula relating the weight of the patient to the dose that is required to be delivered and the rate of infusion required to deliver that dose. An example is provided in Box 1.

The "Rule of Six"
6mg/kg of Drug X in 100ml Diluent Y Infusion rate of 1mL/hr = 1microgram/kg/minute
Practical example: Morphine Standard starting dose = 20microgram/kg/hr Desired initial infusion rate = 1mL/hr
1mg/kg morphine sulphate in 50mL 0.9% sodium chloride Concentration = 20micrograms/kg/mL Infusion rate = 1mL/hr

Box 1 - The Rule of Six 1

It has been demonstrated that the use of weight-based dilutions for infusions leads to unavoidable inaccuracy. Parshuram demonstrated that in opiates prepared using the RoS in a single children's hospital in North America found that 65% of infusions were >10% variant from the expected concentration (11). Furthermore in simulated studies it has been identified that these discrepancies are independent of experience or professional background of the operator or the frequency with which the task is undertaken (12). These studies have been replicated in other intensive care contexts (13) and in other healthcare organisational contexts (14).

Aguado-Lorenzo identified that the variation of products prepared in controlled pharmaceutical environments was lower than those prepared at ward level, and recommended that infusions should be prepared centrally (14). This supports the recommendations from the National Patient Safety Agency (NPSA), that those high-risk

intravenous medicines should be prepared in controlled pharmacy environments and provided in ready to use solutions (4).

Complexity

Complexity relates in part to the accuracy of preparation and therefore the contributing factors to errors in accuracy will overlap into the errors associated with complexity. However, there are additional issues around complexity that do not manifest in the accuracy of preparation.

The use of the RoS for paediatric infusions was proposed in the analogue era, before syringe drivers and electronic drug calculators. It was developed for manual infusion administration through drip chambers, and latterly for use in the mechanical gravimetric infusion devices of the late 20th century. It provided a simple arithmetical method for calculating an infusion prescription to ensure that the intended dose was administered in round 1ml aliquots, and for easy titration in these inaccurate systems (15).

It has been demonstrated that the use of the RoS predisposes orders to error (16,17) and these prescribing errors are often propagated into administration errors (18). Thus while the RoS is proposed to enable rapid prescription of urgent medications, these prescriptions are often wrong, and in the advent of digital infusion systems with stated accuracy of 0.07ml/hr (19) it is difficult to justify the continuing use of RoS.

Efficiency

The overwhelming institutional drive to improve intravenous medication safety is also supported by an increasing drive towards operational efficiency. The NHS is in the midst of the biggest financial squeeze in a generation with services expected to do more within the same resource. The continuing use of bespoke weight based infusions in paediatric care is cumbersome and slow. In small scale single centre studies it is estimated that a single syringe consumes 40 minutes of nursing time to prepare (20,21). By using fixed concentration infusions this resource use has been reported as being reduced by up to 75% (21–24) as well as reducing medication errors (25).

It is postulated that by using ready to use solutions (pre-filled syringes or vials) this time to administration of medication to patients can be reduced even further to 5 minutes, or by >80% (21,26). This can only be delivered with commercially available solutions or through the use of central pharmacy preparation. The RoS cannot be effectively deployed in commercial or controlled pharmaceutical environments as they still require the individual manipulation of products and equipment to deliver a bespoke solution (with the associated accuracy issues described previously). Thus the use of fixed concentrations is the only method that can ensure that solutions are delivered at an appropriate time, and with suitable accuracy.

Standardising (Fixed) Concentrations

The most effective intervention to mitigate these issues is the use of standard, or fixed, concentrations. Standardisation of infusions was first recommended by Keeling in adult intensive care in the UK as a mechanism to harmonise practice and improve patient safety (27). With the development of a national consensus on concentrations, 90% of UK adult intensive care units now use the recommended concentrations (28).

In paediatric care this is less well defined. The Joint Commission (JC) in the United States recommended that infusion practice should be standardised across paediatric care in 2004 (29). The JC never proposed a definition of "standardised" and thus states and institutions have standardised but in a non-standard way. To assist adoption, the Institute of Safe Medication Practice (ISMP) generated a list of high-alert drugs and concentrations in 2008 for Neonatal care (30) and for opiates in Canada (31). Adoption of these is uncertain. Because of this definitional ambiguity, this report will refer to Fixed Concentration Infusions (FCI) rather than standardised concentrations.

In the Republic of Ireland, the implementation of a single national electronic prescribing system in paediatric intensive care units (PICU) triggered the drive towards FCI. Subsequently, FCIs have been successfully implemented across both PICUs in the country (32). Electronic prescribing is a strong driver for patient safety and medication error

reduction in the UK and therefore FCIs should also be considered an important part of service development in this context as well.

Thus there is a clear drive towards standardisation as a move both to maintain and improve patient safety but also to deliver care more efficiently. However, localised solutions to these do not achieve the benefits that are expected and lead to care being provided with just as much (if not more) variation than had been delivered previously. The experience of adult intensive care demonstrates that if there is a single suite of recommendations, then there is more impetus for those standards to be adopted. Therefore in neonatal and paediatric care there is a clear need for a national consensus on fixed concentration infusions in order to support organisational uptake of this intervention.

Aims and Objectives

This project seeks to define a consensus on medication concentrations for the twenty most commonly infused medicines in paediatric and neonatal care. This consensus MUST include morphine.

This outcome will be achieved by:

- Taking the range of concentrations defined in a previous scoping survey as the initial concentration framework
- Use a modified Delphi technique to arrive at the desired consensus from paediatric professionals
- Agree those products that do not arrive at consensus using a conference focus group technique

Methods

This project seeks to influence and change practice, and drive practice in a standardised direction. The MRC guidance for development of complex interventions (33) was used to inform the design of this study. The framework of initial concentrations was developed in a scoping study in the summer of 2016 and is outlined in Table 1 and served as the foundation of the initial consultation.

Survey design

The Delphi technique was selected as it is a robust method for permitting experts to express their preference and for researchers to identify fields of commonality (34).

The survey was developed to identify the preferences of professionals for concentrations of 37 drugs over 6 age groups. Age groups were not defined explicitly, but the concentration preferences were elicited using simple case scenarios, emulating a methodology developed by Arenas-Lopez (26). These scenarios are presented in Appendix I. Due to significant variability in the definition of age groups and the as-yet undefined nature of weight bands in paediatric care, the decision was made to base concentration assessment on fluid load that each concentration presented to the patient. The acceptable limit of fluid volume was set arbitrarily at 5ml/kg/day following discussion with clinical experts in an Expert Advisory Group (EAG).

Consensus definition

The threshold for consensus was set at 70% agreement over two concentrations in each drug and age range. The survey was designed and constructed initially using a university-hosted survey engine (ClassApps LLC, Kansas City, USA) and was tested among the research team and the EAG prior to launch. Due to issues with multi-platform compatibility and the heavy programme code burden of design in the first cycle, the management team made the decision to utilise a third-party survey platform for the second round of the survey (SurveyMonkey®, San Mateo, USA).

Table 1 - Initial concentration framework for Survey I

Drug	Stock solution	NICU		Paediatric			Adult	Notes
Sedation								
Morphine	10mg/ml	40 mcg/ml	100 mcg/ml	200 mcg/ml		1 mg/ml	1-2mg/ml	Adjusted to reflect NIC feedback
Fentanyl	50microgram/ml	50mcg/ml					50mcg/ml	Can we make this more concentrated for higher doses?
Midazolam	5mg/ml	200 mcg/ml	500 mcg/ml			5 mg/ml	1-2mg/ml	Adjusted to reflect EAG feedback
Clonidine	150microgram/ml	3 mcg/ml		6 mcg/ml	12 mcg/ml	24 mcg/ml	15mcg/ml	Adjusted to reflect EAG feedback
Ketamine	50mg/ml	1mg/ml		5mg/ml	10mg/ml		10mg/ml	Adjusted with EAG feedback

Drug	Stock solution	NICU	Paediatric		Adult	Notes
Cardiovascular support						
Noradrenaline	1mg/ml	30 mcg/ml	60 mcg/ml	120 mcg/ml	80, 160, 320microgram/ml	Adjusted to reflect EAG feedback. The Delphi will offer adult and proposed paed concs as choices
Adrenaline	1mg/ml	30 mcg/ml	60 mcg/ml	120 mcg/ml	Not included in ICS guidelines	
Dobutamine	12.5mg/ml	600 mcg/ml	1.2 mg/ml	2.4 mg/ml	5mg/ml	Adjusted to reflect EAG feedback.
Dopamine	40mg/ml	600 mcg/ml	1.2 mg/ml	2.4 mg/ml	4-8mg/ml	Adjusted to reflect EAG feedback.
Isoprenaline						Removed from panel – unlicensed medicine with unstable supply
Furosemide	10mg/ml	1mg/ml	2mg/ml	10 mg/ml		
Labetalol	5mg/ml	1mg/ml		5mg/ml	5mg/ml	Adjusted with EAG feedback
Milrinone	1mg/ml	100mcg/ml		200mcg/ml	200mcg/ml	
Vasopressin	20unit/ml	0.4unit/ml			0.4units/ml	
Glyceryl trinitrate	1mg/ml	1mg/ml			1mg/ml	
Sodium nitroprusside	25mg/ml	1mg/ml				
Amiodarone (Peripheral conc)	50mg/ml	1mg/ml				Adjusted to reflect EAG feedback
Amiodarone Load		3mg/ml			6mg/ml	
Amiodarone Maint		3mg/ml		6mg/ml	6, 12, 18mg/ml	
Epoprostenol						Removed from panel – rarely used.

Drug	Stock solution	NICU	Paediatric		Adult	Notes
PDA Maintenance						
Dinoprostone (Choice 1)	1mg/ml	1mcg/ml for doses <50ng/kg/min 10mcg/ml for doses >50ng/kg/min			-	Adjusted to reflect EAG feedback. Both choices will be offered in Delphi
Dinoprostone (Choice 2)	1mg/ml	1mcg/ml for doses <40ng/kg/min 7.5mcg/ml for doses >40ng/kg/min				
Alprostadil	500microgram/ml	6mcg/ml			Not applicable	
Neuromuscular blockade						
Rocuronium	10mg/ml	2.5mg/ml	5mg/ml	10mg/ml	10mg/ml	Adjusted to reflect EAG feedback.
Vecuronium	2mg/ml	200mcg/ml	1mg/ml	2mg/ml	1-2mg/ml	
Atracurium	10mg/ml	2.5mg/ml	10mg/ml			
Anticoagulants						
Heparin **(systemic anticoagulation only)**	1000units/ml	50 units/ml	200 units/ml	500 units/ml	1000units/ml	

Endocrine and Electrolyte replacement						
Magnesium	2mmol/ml	0.4mmol/ml			0.4mmol/ml	
Calcium (central)	0.224mmol/ml	0.224 mmol/ml				
Calcium (peripheral)	0.224mmol/ml	0.045 mmol/ml				Included on EAG feedback
Potassium chloride	2mmol/ml	0.3mmol/ml 0.4mmol/ml OR 0.5mmol/ml				Adjusted with EAG feedback – all choices presented in Delphi
Sodium chloride	2.7% polyfusor = 0.45mmol/ml	0.45mmol/ml OR 0.3mmol/ml OR 0.4mmol/ml OR 0.5mmol/ml OR				Adjusted with EAG feedback – all choices presented in Delphi
Insulin	100units/ml	0.2unit.ml	0.5 unit/ml	1unit/ml	1unit/ml	Adjusted to reflect EAG feedback
Acetylcysteine						Removed from panel

Products that can already be considered "standard" and therefore not submitted to Delphi:

Thiopental	25mg/ml	25mg/ml
Vancomycin	50mg/ml	5mg/ml
Salbutamol (Peripheral)	1mg/ml	200mcg/ml
Salbutamol (Central)	1mg/ml	1mg/ml
Aminophylline (Peripheral)	25mg/ml	1mg/ml
Aminophylline (Central)		10mg/ml
Esmolol	10mg/ml	10mg/ml
Magnesium	2mmol/ml	0.4mmol/ml

Those drugs that reached 70% agreement in the first stage of the survey were considered to have achieved consensus and were removed from further stages. Drugs with an agreement of less than 70% went forward into a second stage. To assist in refinement of these concentrations, the first stage invited participants to suggest alternative concentrations or characteristics of solutions that were then incorporated in the second round of the survey.

Those solutions that achieved consensus in the second stage also went forward to the consensus framework. Those that did not were identified and were then presented to professional working groups at a consensus conference in Manchester in February 2017.

Distribution

The first round of the survey was released to paediatricians, neonatologists, intensivists, nurses and pharmacists in November 2016. A web link was distributed by e-mail through key stakeholders – the Paediatric Intensive Care Society (PICS); the Neonatal and Paediatric Pharmacists Group (NPPG) and the British Association for Perinatal Medicine (BAPM) and the Making it Safer Together (MiST) Collaborative membership. In total approximately 1000 individuals were invited to participate and response rate was calculated from this figure. The same stakeholders were used to distribute the survey in stage 2.

Consensus conference

A consensus conference was held as part of the annual MiST collaborative conference in February 2017. The aim of this conference was to provide respondent validation of the final consensus statement and to discuss those drugs in the second stage that still did not achieve consensus. 68 healthcare professionals and experts in patient safety attended and were divided into four working groups. Membership of the working groups was randomised using a sequential allocation based on the attendance list. This ensured that groups were balanced for attendees and prevented self-selection based on perceived importance of specific drugs. Working groups were allocated the following drugs:

1. Sedation and Analgesia – morphine, midazolam, fentanyl, clonidine, ketamine
2. Cardiovascular 1 – noradrenaline, adrenaline, furosemide, vasopressin, amiodarone

3. Cardiovascular 2 – dobutamine, dopamine, labetalol, glyceryl trinitrate, sodium nitroprusside, dinoprostone
4. Anaesthesia and Haemostasis – rocuronium, vecuronium, atracurium, insulin, heparin, potassium chloride

Each working group was facilitated by a member of the management group or a MiST co-ordinating committee member. Members of each workshop were presented with 5-6 drugs (Appendix II-V) from the consensus framework arrived at in Figure 2, and were asked four questions:

1. Are all these concentrations able to be infused in a broad range of scenarios?

2. Do any of the concentrations result in excess fluid volumes in some scenarios?

3. Would you be happy to use these concentrations in your practice?

4. What changes would you like to make (if any) to improve the utility of the concentrations proposed?

The purpose of the workshops was to enable debate about the concentrations that the surveys had produced, and to subject them to table top exploration among experts as to the utility of these concentrations. Discussions and changes were recorded by the facilitator on a standardised proforma (Appendix VI). In common with the consensus definition used throughout the study, consensus in the final stage was defined as >70% of attendees in favour of the range of concentrations proposed.

Study Management and Ethical Considerations

The study was overseen by a four-man management group made up of senior pharmacists from London, the midlands and the North West. To support the development of study materials and ensure that the voice of the multidisciplinary team was incorporated into the study, there was an active Expert Advisory Group (EAG) consisting of clinicians, nurses and pharmacists from all fields of paediatric and neonatal care.

The study was reviewed by the R&D department of Central Manchester University Hospitals NHS Foundation Trust who designated this study as service improvement and the need for formal ethical review was thus waived.

Results

Two iterations of the survey were circulated to respondents. The first iteration was circulated between October and November 2016, and the second iteration was circulated in January 2017. Demographics and response rates are presented in Table 2.

	Survey I	**Survey II**
Total Responses (1000 circulees via e-mail) (Rate)	65 (6.5%)	53 (5.3%)
Completion rate	26% (17/65)	32% (17/53)
Background	Medic: 16 (31%) Nurse: 15 (29%) Pharmacist: 21 (40%)	17 (33%) 13 (25%) 22 (42%)
Region	England: 49 (96%) Scotland: 2 (4%) Wales: 0 NI: 0	43 (86%) 3 (6%) 3 (6%) 1 (3%)
Practice	PICU: 29 (56%) NICU: 12 (23%) Theatres: 2 (4%) Transport: 4 (8%)	36 (75%) 10 (21%) 1 (2%) 1 (2%)

Table 2 - Survey responses

Survey I

In the first round of the survey, 24 drugs were presented with 6 scenarios (144 discrete questions). Consensus was achieved in 67 scenarios (46.5%) and a consensus was identified in 17/24 (70.8%) drugs (Table 3). The scenarios that achieved consensus were predominantly those that represented older children (>10kg)

Table 3 - Survey 1 results. Fields highlighted in red represent consensus

Drug	0.5kg	1.2kg	4kg	10kg	25kg	40kg
Morphine	40mcg/ml 100mcg/ml 200mcg/ml		100mcg/ml 200mcg/ml		200mcg/ml 1mg/ml	
Fentanyl	20mcg/ml 50mcg/ml			ACCEPT 50MCG/ML		
Midazolam	200mcg/ml 500mcg/ml		500mcg/ml 5mg/ml			
Clonidine	3mcg/ml 6mcg/ml 12mcg/ml	6mcg/ml 12mcg/ml	6mcg/ml 12mcg/ml 24mcg/ml		12mcg/ml 24mcg/ml	
Nor/Ad	30mcg/ml 60mcg/ml	30mcg/ml 60mcg/ml 80mcg/ml	30mcg/ml 60mcg/ml 80mcg/ml 120mcg/ml	60mcg/ml 80mcg/ml 120mcg/ml 160mcg/ml	120mcg/ml 160mcg/ml 320mcg/ml	
Dop/Dob	600mcg/ml 1.2mg/ml	600mcg/ml 1.2mg/ml 2.4mg/ml		ACCEPT 1.2mg/ml 2.4mg/ml		
Furosemide	1mg/ml 2mg/ml		1mg/ml 2mg/ml 10mg/ml		ACCEPT 2mg/ml 10mg/ml	
Labetalol	1mg/ml 5mg/ml		ACCEPT 5mg/ml	1mg/ml 5mg/ml		ACCEPT 5mg/ml
Milrinone	100mcg/ml 200mcg/ml			ACCEPT 200mcg/ml		
Vasopressin	0.2units/ml is too concentrated			ACCEPT 0.4units/ml		
GTN	100mcg/ml 500mcg/ml				ACCEPT 1mg/ml	
SNP	100mcg/ml 500mcg/ml			ACCEPT 1mg/ml		
Amiodarone		ACCEPT 1mg/ml 3mg/ml		ACCEPT 3mg/ml 6mg/ml		

Dinoprostone	ACCEPT 1mcg/ml for doses <50ng/kg/min 10mcg/ml for doses >50ng/kg/min					
Alprostadil	ACCEPT 6mcg/ml					
Rocuronium	2.5mg/ml 5mg/ml		5mg/ml 10mg/ml			
Vecuronium	200mcg/ml 1mg/ml;		1mg/ml 2mg/ml			
Atracurium	No consensus			ACCEPT 10mg/ml		
Heparin	50units/ml	50units/ml 200units/ml	No consensus	200units/ml 500units/ml	ACCEPT 500units/ml	
Insulin	No consensus		0.5units/ml 1unit/ml	ACCEPT 1unit/ml		
Magnesium	No consensus		ACCEPT 0.4mmol/ml			
Calcium gluconate	0.224mmol/ml 0.045mmol/ml	ACCEPT 0.224mmol/ml				
Potassium chloride	0.4mmol/ml 0.5mmol/ml					
Sodium chloride	No consensus		0.4mmol/ml 0.5mmol/ml	0.5mmol/ml	0.4mmol/ml 0.5mmol/ml	0.5mmol/ml

Four products were removed entirely from the consensus framework at this stage. Electrolytes (sodium, magnesium, calcium) were removed because free text responses in the first survey indicated that there may be a risk of inappropriate incursion into other fields of practice. Alprostadil was removed because it had a single concentration quoted that was very low, and very few members of the EAG were familiar with its use.

Survey II

Thus 20 drugs and 46 scenarios went forward into the second survey. Subsequently, consensus was achieved in 34/46 scenarios (73.9%) and 19/20 (95%) drugs presented (Table 4). Those scenarios that did not achieve consensus were relevant to neonatal care only, and went forward for further discussion at the consensus conference.

Table 4 - Survey II results. Field highlighted in red represent those solutions that did not achieve consensus

Drug	**Pre term infants**	**Infants**	**Children**	**Adolescent**	**Adult**(27)
Morphine	40 or 100microgram/ml	100 or 400microgram/ml	400microgram/ml	1mg/ml	1 or 2mg/ml
Midazolam	200microgram/ml		500microgram/ml	5mg/ml	1 or 2mg/ml
Fentanyl	10microgram/ml	20microgram/ml	50microgram/ml		50microgram/ml
Clonidine	3microgram/ml	6microgram/ml	12microgram/ml	24microgram/ml	15microgram/ml
Ketamine	1mg/ml	5mg/ml or 10mg/ml			10mg/ml
Nor/Adrenaline	5microgram/ml or 20microgram/ml	20 microgram/ml or 80microgram/ml	160microgram/ml	320microgram/ml	80 to 320 microgram/ml
Dop/Dobutamine	600microgram/ml	1.2mg/ml	2.4mg/ml 5mg/ml (central only)		4, 5 and 8mg/ml
Furosemide	1mg/ml	2mg/ml	2mg/ml 10mg/ml (central only)		No recommendation
Labetalol	1mg/ml	5mg/ml			Commercially available 5mg/ml product
Milrinone	100microgram/ml	200microgram/ml	200microgram/ml 1mg/ml (central only)		200microgram/ml
Vasopressin	0.2units/ml	0.4units/ml			0.4units/ml
Glyceryl Trinitrate	100microgram/ml	1mg/ml			No recommendation
Sodium nitroprusside	250microgram/ml	1mg/ml			No recommendation
Amiodarone	3mg/ml		6mg/ml		3 to 18mg/ml
Dinoprostone	1microgram/ml for doses <50nanogram/kg/minute; 10microgram/ml for doses >50nanogram/kg/minute (central only)		Not indicated in this age group		No recommendation
Rocuronium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation

Vecuronium	200microgram/ml or 400microgram/ml		1mg/ml 2mg/ml	1 or 2mg/ml
Atracurium	2.5mg/ml		10mg/ml	No recommendation
Heparin	50units/ml or 100units/ml	100units/ml or 200units/ml	500units/ml	1000units/ml
Insulin	0.2units/ml	0.5units/ml	1unit/ml	1unit/ml
Potassium chloride	0.3mmol/ml		0.5mmol/ml	No recommendation

Consensus Conference

Attendees were grouped into workshops as described in the methods. The results are presented grouped by workshop.

Workshop 1 – Analgesia and Sedation

DRUG	Pre-term infants	Infants	Children	Adolescent	Adult
Morphine	40 or 100microgram/ml	100 or 200microgram/ml	400microgram/ml	1mg/ml	1 or 2mg/ml
Fentanyl		20microgram/ml	50microgram/ml		50microgram/ml
Midazolam	200microgram/ml		500microgram/ml	1 or 2mg/ml	
Clonidine	6microgram/ml		12microgram/ml 40microgram/ml		15microgram/ml

There was no consensus agreed for morphine for pre-term infants and it was recommended that this should be put to a binary choice to all attendees of the consensus conference. The professionals also recommended a 4-fold increase in concentration for those patients classed as infant and child (as this would reflect the four-fold variation in weights between these groups from ~4kg to ~20kg.) Fentanyl was removed from pre-term infant recommendations as it is unlikely to be used in this population. The upper concentration of midazolam was adjusted to come in to line with adult recommendations. Clonidine concentrations were considered too dilute in the upper age ranges, therefore an alternative regime was proposed and accepted. It was recommended that ketamine should be removed as it has diverse uses and complex dosing depending on indication and to propose a single standardised system would be unsafe to implement.

Workshop 2 – Cardiovascular I

DRUG	Pre-term infants	Infants	Children	Adolescent	Adults
Nor/Adrenaline	5 microgram/ml	40 microgram/ml	160 microgram/ml		80 to 320 microgram/ml
Furosemide	1mg/ml	2mg/ml	2mg/ml 10mg/ml (central only)		No recommendation
Milrinone	100 microgram/ml	200 microgram/ml	200 microgram/ml 1mg/ml (central only)		No recommendation
Vasopressin	0.2units/ml	0.4 units/ml			0.4units/ml
Amiodarone	3mg/ml		6mg/ml		3 to 18mg/ml

The workshop accepted four of the five drugs without changes. With noradrenaline and adrenaline it was suggested that for preterm infants a lower concentration would facilitate

titration of dosing. Some concern was expressed relating to fluid load, but this was ameliorated by adjusting the next concentration increment. The proposed concentrations were 20 or 80microgram/ml but the group accepted 40microgram/ml (an 8-fold change from the lower increment, and a four-fold increment to the higher concentration.) This also maintained consistency with solutions already recommended by adult care.

Workshop 3 – Cardiovascular II

DRUG	Pre-term infants	Infants	Children	Adolescents	Adults
Dopamine	1.2mg/ml		2.4mg/ml 5mg/ml (central only)		4, 5 and 8mg/ml
Dobutamine	1.25mg/ml		5mg/ml		5mg/ml
Labetalol	1mg/ml	5mg/ml			5mg/ml
Dinoprostone	1microgram/ml for doses <50nanogram/kg/min 10microgram/ml for doses >50nanogram/kg/min		Not indicated for this group		No recommendation

The group unanimously agreed that glyceryl trinitrate should be removed from the framework. It is used only very rarely and there is little evidence to support its efficacy. The group also agreed that sodium nitroprusside should be removed. As an unlicensed medicine in the UK and with a very limited clinical envelope of use, it was unlikely to be adopted widely. This approach had already been taken when developing the initial consultation framework, when the decision was made to remove isoprenaline from review as it too was an unlicensed medicine with an unstable supply route.

Dopamine and dobutamine concentrations were adjusted to reflect the availability of stock solutions in the UK (dopamine hydrochloride 80mg/ml and dobutamine hydrochloride 12.5mg/ml and 5mg/ml). This ensured whole-millilitre manipulations, and continuity with adult recommendations.

There was a perceived risk of ten-fold error with dinoprostone as proposed. However there was an acknowledged need for some standardised approach to dinoprostone. It was recommended that the current proposals be expanded out to the attendees of the conference as a whole.

Workshop 4 – Anaesthesia and haemostasis

DRUG	Pre-term infants	Infants	Children	Adolescent	Adult
Rocuronium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation
Vecuronium		400microgram/ml	1mg/ml 2mg/ml		1 or 2mg/ml
Atracurium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation
Heparin	100units/ml		500units/ml		1000units/ml
Insulin	0.2units/ml		1unit/ml		1unit/ml
Potassium chloride	0.5mmol/ml				No recommendation

The most frequently used muscle relaxants within the group were rocuronium and atracurium and there was unanimous agreement that these should have similar dilutions across the framework because they were administered at similar doses (300-1000microgram/kg/hr). Vecuronium in pre-term infants was removed from the framework as there was insufficient expertise in its use in this age-group.

Potassium chloride was presented as a binary choice between 0.3mmol/ml and 0.5mmol/ml and a simple vote was taken among workshop attendees. 100% (14/14) of participants agreed on 0.5mmol/ml as the concentration of choice.

Heparin concentrations were decided on the basis of infusibility at the range of doses used in clinical practice (10-35units/kg/hr) and the group were able to agree on two concentrations that complemented the adult recommendations. Insulin concentrations were deliberated with the same considerations and two concentrations were agreed unanimously.

Survey III

Through the consensus workshop, it was identified that there was a need for a further survey to make final decisions on the following drugs and concentrations:

1. Morphine 40microgram/ml, 100microgram/ml and 400microgram/ ml for pre-term and term infants (scenarios 1 and 2)
2. Clonidine for ratification of the alternative dilutions – 6microgram/ml, 12microgram/ml and 40microgram/ml
3. Ratification of dinoprostone 1microgram/ml and 10microgram/ml

The survey was circulated among consensus conference attendees only (n=68) and the response rate was 19.1% (13/68). The choices were presented as binary "Yes/No" options and the results are presented in Table 2.

Option		**Outcome**
Morphine for low-birthweight pre-term infants		
40microgram/ml	8/13 (61.5%)	No consensus. Removed from framework
100microgram/ml	5/13 (38.5%)	
Morphine for term infants		
100microgram/ml	9/13 (69.2%)	Consensus achieved.
200microgram/ml	4/13 (30.8%)	
Dinoprostone – Are the proposed concentrations appropriate? *(1 respondent skipped the question)*		
Yes	8/12 (66.7%)	No consensus. Removed from framework
No	4/12 (33.3%)	
Clonidine – Are the proposed concentrations appropriate? *(1 respondent skipped the question)*		
Yes	11/12 (91.7%)	Consensus achieved.
No	1/12 (8.3%)	

Table 5 - Results of survey III

The low response rate presented a challenge in determining where consensus had been achieved. In the case of morphine for term infants, a single additional positive answer would have raised the percentage agreement from 69.2% to 76.9% therefore the management group agreed to round the percentage up from 69 to 70%. Furthermore, in the case of dinoprostone a single additional positive response would have increased the percentage agreement from 66.7% to 75%. However, it was harder for the management group to justify rounding the percentage value, therefore it was agreed to maintain dinoprostone as unagreed.

Final Consensus Framework

Drug	Pre term infants	Infants	Children	Adolescent	Adult(27)
Morphine		100microgram/ml	400microgram/ml	1 or 2mg/ml	
Midazolam	200microgram/ml		500microgram/ml	1 or 2mg/ml	
Fentanyl		20microgram/ml	50microgram/ml		
Clonidine	6 microgram/ml		12microgram/ml; 40microgram/ml		15microgram/ml
Nor/Adrenaline	5microgram/ml	40 microgram/ml	160microgram/ml		80 to 320 microgram/ml
Dopamine	1.2mg/ml		2.4mg/ml 8mg/ml (central only)		4, 5 and 8mg/ml
Dobutamine	1.25mg/ml		5mg/ml		5mg/ml
Furosemide	1mg/ml	2mg/ml	2mg/ml 10mg/ml (central only)		No recommendation
Labetalol	1mg/ml	5mg/ml			Commercially available 5mg/ml product
Milrinone	100microgram/ml	200microgram/ml	200microgram/ml 1mg/ml (central only)		200microgram/ml
Vasopressin	0.2units/ml	0.4units/ml			0.4units/ml
Amiodarone	3mg/ml		6mg/ml		3 to 18mg/ml
Rocuronium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation
Vecuronium		400microgram/ml	1mg/ml		
Atracurium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation
Heparin	100units/ml		500units/ml		1000units/ml
Insulin	0.2units/ml		1unit/ml		1unit/ml
Potassium chloride	0.5mmol/ml				No recommendation

Those boxes in black are those solutions where consensus could not be achieved.

Discussion

We believe that this is the first consensus on fixed concentration infusions developed using robust methods within a complex centralised healthcare system that has used the opinions and perceptions of healthcare providers as central to its development.

Comparison with other frameworks

It is interesting to note that many of the concentrations proposed for older infants and children were accepted in the first round. The areas of debate were for those patients who would be considered at the extremes of care – older adolescents and pre-term, low birthweight infants. During the workshops at the consensus conference the focus of discussion was on the fluid load that each concentration presented to patients of varying weights. This would support the position of this project that the concentration itself is of little importance, but it is fluid burden that is presented to the child that is of importance. However, this study also identified that there are issues with the infusibility of solutions at lower doses which has resulted in very low concentrations for some solutions (e.g. adrenaline and noradrenaline.)

Furthermore, it is noted that the ISMP recommendations for neonatal care (30) recommend similarly low concentrations for neonatal care (summarised in Table 6)

Drug	ISMP Concentration	MiST Concentration
Morphine	100microgram/ml	100microgram/ml (infants)
Midazolam	500microgram/ml	200microgram/ml
Fentanyl	10microgram/ml	20microgram/ml
Noradrenaline	16microgram/ml	5microgram/ml
Adrenaline	10microgram/ml	5microgram/ml
Dopamine	1.6mg/ml	1.2mg/ml
Dobutamine	2mg/ml	1.25mg/ml
Furosemide	2mg/ml	1mg/ml
Insulin	0.1unit/ml	0.2units/ml

Table 6 - Comparison of MiST Infusions for Neonates with ISMP neonatal recommendations

The fact that there is considerable similarity between our recommendations and the recommendations of the ISMP gives assurance that this consensus framework is valid. However testing of this intervention is recommended in practice to robustly evaluate the true utility of these concentrations.

This framework has produced an average of 2.3 concentrations per drug, where other studies have attempted to utilise only one or two (24,30) however it has been accepted that a uni- or bi-lateral choice would be unsafe in a population where weight varies so significantly (from 0.5 to >100kg) and the "optimum" number of FCIs has been posited as two to four (35). Conversely, some studies have used a great many more (36) but these have been in single centres where control and delivery can be supervised directly by the researchers. In seeking a national framework, this would be unwieldy and unattractive to centres seeking to implement such a system. Thus this project has delivered a range of concentrations that reflects the current research available.

With regards to patient weight, almost all the studies in the literature seek to define the weight bands that should be used as part of the FCI framework. This study has very deliberately not sought to set this out. During piloting of the initial survey instrument with the EAG it rapidly became clear that clinicians were focussing more on the suggested weight bands than on the utility of the medications themselves. This is an experience reported by Perkins et al. in their single centre FCI implementation project (26) and their solution was to assess the concentration preferences on the basis of scenarios instead of suggested weight bands. We have built on this work, and demonstrated that it can be used on a much larger scale to achieve consensus on FCIs at a national level.

Limitations

As with all research, this study is not without its limitations. The absence of anaesthetic input is notable. The respective representative groups of anaesthetists in the UK were approached but did not engage with the project. However, there was a paediatric anaesthetist on the EAG and a core stakeholder was the UK Paediatric Intensive Care Society (PICS) who are a special interest group of the Association of Anaesthetists of Great Britain and Ireland and count a number of anaesthetists in their membership. Given the lack of

formal engagement from anaesthetists it is impossible to say that this consensus covers those professionals working in an operating theatre environment. However we posit that this can serve as a useful framework for future development work.

The response rate in all stages of the survey is extremely low at around 6% for Surveys I and II and 20% in Survey III. There was also a high attrition rate during attempts at the survey with 70 to 75% of respondents failing to complete it in full. This reflects the size of the survey and the degree of mental effort required to complete it. By definition, complex calculations were required in order to make reasoned judgements about the infusion choices, and despite us providing a validated calculation tool to respondents, completion rate was still poor. A review by Sheehan of e-mail surveys posits a number of reasons for this low response rate (37):

1. Surveys in excess of 10 questions tend toward a lower response rate with only 32% returned
2. Issue saliency determines to an extent how respondents will engage with a subject. If respondents have no strong opinions on a subject, or don't feel it applies to them then response rate will be lower.

It could thus be argued that as a very large and complex survey it was probable that a low response rate and high-attrition rate would be encountered, however there was no other way such a complex and nuanced issue could be approached. Attrition rate however cannot simply be put down to respondents losing interest in the survey. It is likely that a number of respondents did not have sufficient experience of certain drugs or scenarios (e.g. a neonatal nurse responding to scenarios involving adolescents) and instead chose to skip questions where they could. In both Survey I and II, questions were designed to require answers in all available scenarios therefore driving respondents to skip whole questions.

However, a meta-analysis of web-based survey responses suggests that sample representativeness may be more important than response rate (38). In our demographic analysis for both Survey I and Survey II we have an even representation of medical, pharmacy and nursing staff with clinical staff accounting for at least 60% of responses in

each cycle. Our results are therefore likely to be representative which adds strength to our findings in the face of a low response rate.

Of utmost importance however is that this is a proposed framework of concentrations. They have not been subjected to rigourous testing in practice which will inevitably lead to changes and adjustments. This has been evidenced in the experience of colleagues in the Republic of Ireland (32) who have made adjustments to their national framework for infusions several times over the last five years. However, as with any new service development, there must first be a proposed framework which can then form the basis of testing and further study in order to identify the most practical solution.

Plans for future research

This framework marks the beginning of a long programme of development and implementation. It is not intended to be viewed as a stand-alone document that can be used in isolation. While FCIs are advocated as an important intervention to improve medication safety, the mechanisms of this improvement are uncertain. During the consensus conference and workshops it was possible to capture a number of legitimate concerns relating to this intervention that must be explored and scrutinised. Therefore we propose the following future research:

Human factors assessment of infusions

Prescribing, preparation and administration of infusions is a complex process that is associated with substantial cognitive burden. Current mechanisms for prescribing and preparation place multiple checks prior to administration that mitigate the potential for administration error and harm. Apkon and colleagues have demonstrated using human factors (HF) assessment techniques that these processes themselves contribute to errors (22). However, this has been refuted by Brannon who posits that FCIs may increase the risk of administration errors by reducing the number of checks prior to administration of the infusion (39) effectively moving risk proximal to the patient.

The study of medication administration errors to date has been poor, but with developing human factors methodology and observational techniques our understanding of the causes of these errors is increasing. It is therefore recommended that a multi-centre observational study to capture the processes involved in, and the causes and outcomes of, infusion administration errors in paediatric care using suitable HF methods be undertaken to robustly assess the risks and propose mitigating interventions.

Within any HF study the perspectives and views of practitioners are critical to the understanding of how errors emerge. Error causation is non-linear, and related directly to the context in which the errors occur, therefore within this HF study there must be a strong qualitative element to capture these complex sociotechnical influences. The outcomes of this wide-ranging HF study should be:

- To identify a process to be followed to support implementation of FCIs in any organisation
- To outline the educational and support tools that should be available to support the safe implementation of FCIs
- Provide risk assessment materials to enable organisations to robustly manage the implementation of FCIs within their organisations.

Commercialisation

An important intended outcome of the development of this framework is the possibility of commercialisation of the recommended solutions. Current recommendations are for infusions to be provided in ready-to-use forms however individual hospitals and provider organisations lack capacity to provide this en masse, and such a disjointed provision would be inherently inefficient. It is also equivocal as to what the most appropriate final container should be. There are reports in the literature that pre-filled syringes are the preference of practitioners in the clinical area (40) however syringes are difficult to manage from a pharmaceutical and risk perspective. A recent study in a single British ICU identified that syringes presented an irreconcilable risk of selection error (25) and further recommendations have been made regarding the use of pre-filled terminally sterilised vials (41).

Given the ambiguity at present of the most appropriate presentation of these solutions a collaborative approach is recommended between industry, NHS Specialised Services and clinicians, nurses and pharmacists to explore the strengths and weaknesses of available options and to make recommendations as to the most efficient, cost-effective and acceptable presentations to pursue.

Conclusions

This report presents the first UK-wide consensus framework on infusions for use in paediatric and neonatal care. It is different from other internationally reported frameworks in that it has directly involved clinicians, nurses and pharmacists in its development. Thus it is more robust than those frameworks established by expert committees.

This framework presents opportunities in the reduction of medication error with high-risk medicines by providing support for NHS organisations to implement fixed concentration IV medication systems. It also provides opportunities for the development of commercial, high-quality medicines for use in paediatric care which may become cost-effective through the benefits of volume purchasing.

However, there is still a long way to go before this can be expected to be implemented across the NHS. A programme of research to explore the risks associated with FCIs and the barriers to implementation and commercialisation must be undertaken. It is also recommended that implementation be evaluated robustly using controlled multi-centre studies across a variety of care contexts.

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Appendix I – Clinical Scenarios

Scenario 1 500g preterm neonate with a fluid allowance of 100ml/kg/day

Scenario 2 1200g preterm neonate with a fluid allowance of 90ml/kg/day

Scenario 3 4kg term infant with a fluid allowance of 50ml/kg/day

Scenario 4 10kg child with a fluid allowance of 1000ml/day

Scenario 5 25kg child with a fluid allowance of 1750ml/day

Scenario 6 40kg adolescent with a fluid allowance of 2000ml/day

Appendix II – Workshop 1

MiST Standardisation Working Group
Consensus Summit
February 24th 2017; Royal Manchester Children's Hospital

CONSENSUS ROUND TABLE 1:
SEDATION AND ANALGESIA

DRUG	Pre-term infants	Infants	Children	Adolescent	Adult
Morphine	40 or 100microgram/ml	100 or 400microgram/ml	400microgram/ml	1mg/ml	1 or 2mg/ml
Fentanyl	10microgram/ml	20microgram/ml	50microgram/ml		50microgram/ml
Midazolam	200microgram/ml		500microgram/ml	5mg/ml	1 or 2mg/ml
Clonidine	3microgram/ml	6microgram/ml	12microgram/ml	24microgram/ml	15microgram/ml
Ketamine	1mg/ml	5 or 10mg/ml			10mg/ml

QUESTIONS TO CONSIDER

1. Are all these concentrations able to be infused in a broad range of scenarios?

2. Do any of the concentrations result in excess fluid volumes in some scenarios?

3. Would you be happy to use these concentrations in your practice?

4. What changes would you like to make (if any) to improve the utility of the concentrations proposed?

Appendix III – Workshop 2

MiST Standardisation Working Group
Consensus Summit
February 24th 2017; Royal Manchester Children's Hospital

CONSENSUS ROUND TABLE 2:
CARDIOVASCULAR 1

DRUG	Pre-term infants	Infants	Children	Adolescent	Adults
Nor/Adrenaline	5 or 20 microgram/ml	20 or 80 microgram/ml	160 microgram/ml	320 microgram/ml	80 to 320 microgram/ml
Furosemide	1mg/ml	2mg/ml	2mg/ml 10mg/ml (central only)		No recommendation
Milrinone	100 microgram/ml	200 microgram/ml	200 microgram/ml 1mg/ml (central only)		No recommendation
Vasopressin	0.2units/ml	0.4 units/ml			0.4units/ml
Amiodarone	3mg/ml		6mg/ml		3 to 18mg/ml

QUESTIONS TO CONSIDER

5. Are all these concentrations able to be infused in a broad range of scenarios?

6. Do any of the concentrations result in excess fluid volumes in some scenarios?

7. Would you be happy to use these concentrations in your practice?

8. What changes would you like to make (if any) to improve the utility of the concentrations proposed?

Appendix IV – Workshop 3

MiST Standardisation Working Group
Consensus Summit
February 24th 2017; Royal Manchester Children's Hospital

CONSENSUS ROUND TABLE 3:
CARDIOVASCULAR 2

DRUG	Pre-term infants	Infants	Children	Adolescents	Adults
Dop/Dobutamine	600 microgram/ml	1.2mg/ml	2.4mg/ml 5mg/ml (central only)		4, 5 and 8mg/ml
Labetalol	1mg/ml	5mg/ml			5mg/ml
GTN	100 microgram/ml	1mg/ml			No recommendation
SNP	250microgram/ml	1mg/ml			No recommendation
Dinoprostone	1microgram/ml for doses <50nanogram/kg/min 10microgram/ml for doses >50nanogram/kg/min		Not indicated for this group		No recommendation

QUESTIONS TO CONSIDER

9. Are all these concentrations able to be infused in a broad range of scenarios?

10. Do any of the concentrations result in excess fluid volumes in some scenarios?

11. Would you be happy to use these concentrations in your practice?

12. What changes would you like to make (if any) to improve the utility of the concentrations proposed?

Appendix V – Workshop 4

MiST Standardisation Working Group
Consensus Summit
February 24th 2017; Royal Manchester Children's Hospital

CONSENSUS ROUND TABLE 4:
ANAESTHESIA AND INSULIN

DRUG	Pre-term infants	Infants	Children	Adolescent	Adult
Rocuronium	2.5mg/ml	5mg/ml	10mg/ml		No recommendation
Vecuronium	200 or 400microgram/ml		1mg/ml 2mg/ml		1 or 2mg/ml
Atracurium	2.5mg/ml		10mg/ml		No recommendation
Heparin	50 units/ml or 100units/ml	100units/ml or 200units/ml	500units/ml		1000units/ml
Insulin	0.2units/ml	0.5units/ml	1unit/ml		1unit/ml
Potassium chloride	0.3mmol/ml		0.5mmol/ml		No recommendation

QUESTIONS TO CONSIDER

13. Are all these concentrations able to be infused in a broad range of scenarios?

14. Do any of the concentrations result in excess fluid volumes in some scenarios?

15. Would you be happy to use these concentrations in your practice?

16. What changes would you like to make (if any) to improve the utility of the concentrations proposed?

Appendix VI – Facilitator record

MiST Standardisation Working Group
Consensus Summit
February 24th 2017; Royal Manchester Children's Hospital

WORKSHOP FACILITATION RECORD

WORKSHOP NUMBER		**NUMBER OF ATTENDEES**	
FACILITATOR			

Question number	Comments
1	
2	
3	
4	

FINAL CONCENTRATIONS (Complete at end of discussion)

DRUG	Conc 1	Conc 2	Conc 3	Conc 4

FINAL QUESTION (to be posed at the end of discussions):
DO THE PROPOSED CONCENTRATIONS REPRESENT, IN THE GROUP'S VIEW, A REASONABLE PROPOSAL FOR CLINICAL PRACTICE?
70% of group members must agree.

AGREED		**DISSENT**	