INVESTIGATIONAL MEDICINAL PRODUCT MANUAL

DEXTA

DEXmedetomidine Trial of Adjunct Treatment with Morphine

Manual Version Number: Version 1.0

Manual Version Date: 17-OCT-2025

Sponsor	University Hospitals of Derby and Burton NHS Foundation Trust
IRAS Project ID	1012134

TABLE OF CONTENTS

Revision History

Version	Version date	Summary of amendment
1.0	17 Oct 2025	Not applicable – first version

Abbreviations

Abbreviation	Term
CTU	Clinical Trial Unit
IMP	Investigational medicinal product
ISF	Investigator Site File
MA	Marketing Authorisation
PI	Principal Investigator
SmPC	Summary of Product Characteristics

1. Introduction

This Investigational Medicinal Product (IMP) Manual has been developed to support the consistent implementation of IMP-related procedures for the DEXTA trial (IRAS ID:1012134). It is intended for use in conjunction with the DEXTA protocol, which remains the definitive source of study instructions.

This IMP Manual serves as a reference guide for all delegated site personnel involved in the handling, preparation, and documentation of IMPs. Prior to undertaking any study-related activities, all applicable site staff must receive protocol-specific training, as determined by the sponsor and the Clinical Trials Unit (CTU).

A copy of the manual should be filed in the DEXTA Investigator Site File (ISF). All previous versions should also be retained in the ISF and clearly marked as 'superseded'.

2. Study overview

DEXTA is a three-arm, multi-centre, blinded, randomised, placebo-controlled efficacy trial comparing two dosing regimens of intravenous (IV) dexmedeTOMIDine with placebo, designed to assess whether dexmedeTOMIDine reduces the cumulative dose of morphine administered over 120 hours in ventilated preterm babies.

Babies will be randomised in a 1:1:1 allocation ratio to receive 120 hours of intravenous infusion of:

Intervention 1: DexmedeTOMIDine (**0.5microgram/kg/hour**) + morphine

OR

Intervention 2: DexmedeTOMIDine (**0.25microgram/kg/hour**) + morphine

OR

Comparator: Placebo + morphine

The study will recruit 240 ventilated preterm babies (<32 weeks' gestational age at birth) who are at least 160 hours from birth and require morphine infusion for analgesia.

3. Investigational medicinal products

The IMPs used in the DEXTA trial are defined and described in Table 1.

DexmedeTOMIDine concentrate for solution for infusion is a commercially available medicinal product with a UK marketing authorisation (MA). For this trial, it is relabelled to comply with clinical trial requirements. Its use in the DEXTA trial is considered off-label. To maintain blinding, placebo ampoules are manufactured to be visually indistinguishable from the dexmedeTOMIDine ampoules.

The IMPs are supplied in blinded packs, each identified by a unique Pack ID. Each pack corresponds to one of the three treatment groups and contains seven ampoule pairs (14 ampoules in total), providing sufficient IMP for the full 120-hour infusion period for each baby. The content of each ampoule pair varies depending on the treatment group, as summarised in Table 2.

The preparation of each infusion syringe requires the use of one ampoule pair, with ampoules labelled "XXXX-A" and "XXXX-B". The IMP packs and preparation methods (see section 14) are designed to maintain blinding by ensuring that for babies of the same weight, the volume of IMP administered is consistent across all treatment groups.

Table 1: Descriptions of investigational medicinal products

	DexmedeTOMIDine	**Placebo**
Description of Active Substance	Chemical origin	Chemical origin
Pharmaceutical form	Concentrated solution for infusion	Solution for injection
Composition	200 micrograms of DexmedeTOMIDine in 2mL	2mL of 0.9% Sodium Chloride
Concentration of Active Ingredient	100 micrograms of dexmedeTOMIDine in 1mL	0 micrograms of dexmedeTOMIDine in 1mL
Excipients	Sodium chloride, Water for injections	Sodium chloride, Water for injections
Appearance	Clear, colourless solution	Clear, colourless solution
Unit size	2mL glass ampoule	2mL glass ampoule
Labelling	Commercial label removed and re-labelled in compliance with UK regulatory requirements	Labelled in compliance with UK regulatory requirements
Sourcing	Supplied centrally from the Sponsor via Sharp Clinical Services (UK) Limited	Supplied centrally from the Sponsor via Sharp Clinical Services (UK) Limited

Table 2: IMP packaging configuration of the three types of blinded IMP packs

	DexmedeTOMIDine 0.5microgram/kg/hour	**DexmedeTOMIDine 0.25microgram/kg/hour**	**Placebo**
Outer Carton Contents	7 pairs of 2mL ampoules (Total = 14 ampoules)	7 pairs of 2mL ampoules (Total = 14 ampoules)	7 pairs of 2mL ampoules (Total = 14 ampoules)
Ampoule Pair Composition	2 x active ampoules	1 x active + 1 x placebo ampoules	2 x placebo ampoules

4. IMP supply

IMP will be supplied centrally by the sponsor via Sharp Clinical Services (UK) Limited, who will be responsible for sourcing of dexmedeTOMIDine ampoules and for placebo manufacturing, labelling, and blinding. Final QP certification will be performed by Sharp Clinical Services (UK) Limited; copies will be supplied to sites.

5. Presentation and labelling of IMP

Each IMP pack consists of an outer carton (measuring 6.5 × 10.5 × 2.9 cm) that contains seven inner boxes, each holding a pair of ampoules (14 ampoules in total). All outer cartons and inner boxes are identical in appearance across treatment arms and are labelled in accordance with UK regulatory requirements.

IMP pack containing 7 inner boxes

Inner box showing ampoule pair presentation (two ampoules per pair)

Outer carton label

Protocol: DEXTA IRAS #: 1012134
DexmedeTOMIDine 100 micrograms/mL or Placebo concentrate for solution for Infusion (7 pairs of 2mL ampoules)
For Intravenous use only. See protocol for instructions of use.
Pack ID: VVVV
Batch #: VVVVV Expiry: VVVVVVVVV

Subject initials: .....

Subject ID: ..... Date: .....

Investigator: .....

Site #: .....

Store in original package and protect from light. Store below 25°C. FOR CLINICAL TRIAL USE ONLY. Keep out of the reach and sight of children. Chief Investigator: Shalini Ojha. Sponsor: University Hospitals of Derby and Burton NHS Foundation Trust CTU: Nottingham Clinical Trials Unit, University of Nottingham, Applied Health Research Building, University Park, Nottingham, NG7 2RD, UK. Email: DEXTA@nottingham.ac.uk Tel: 0115 748 58 85 DEX003

Inner box label

Protocol: DEXTA IRAS no: 1012134
DexmedeTOMIDine 100 micrograms/mL or Placebo concentrate for solution for Infusion (One pair of 2ml ampoules)
Batch #: VVVVV Expiry: VVVVVVVVV
Subject ID: ..... Pack ID: VVVV
FOR CLINICAL TRIAL USE ONLY. Sponsor: University Hospitals of Derby and Burton NHS Foundation Trust
DEX002

Ampoule label

Protocol: DEXTA
DexmedeTOMIDine 100 micrograms/mL or Placebo concentrate for solution for Infusion (2ml ampoule)
Batch #: VVVVV
Expiry date: VVVVVVVVV
Pack ID: VVVV-V
Subject ID: .....
FOR CLINICAL TRIAL USE ONLY
Sponsor: University Hospitals of Derby and Burton NHS Foundation Trust.
DEX001

6. Ordering of IMP

Following site activation, the CTU will place an initial order for twelve IMP packs to be delivered to the site's pharmacy. Subsequent shipments, each consisting of six IMP packs, will be managed by the CTU based on site usage and expiry dates.

7. Receipt of IMP

IMP packs will be sent to sites in a temperature-controlled vehicle. Upon delivery,

- Stop the shipment temperature monitoring device.
- Verify the shipment contents against delivery documents.
- Inspect all IMP packs for any evidence of damage.
- Download data from the temperature monitoring device. Print and review data, and check for alarm status.
- If any IMP packs are damaged or the temperature logger shows an alarm, quarantine the affected IMP packs immediately.
    - Notify the CTU by emailing dexta@nottingham.ac.uk within one working day.
    - Follow any additional instructions as per the delivery documents.
    - Do not use the IMP until further instructions are provided.
- Complete the Site Level IMP Accountability Log (Appendix A)
- As soon as possible, arrange for the transfer of the IMP packs to the neonatal unit storage location and document the transfer on the Site-Level IMP Accountability Log (Appendix A).
- Confirmation of receipt in REDCap must **only be carried out after the IMP packs have been transferred** to the neonatal unit storage location (instructions in Appendix B).
- File all documents in the site file.

8. Storage requirements of IMP

The recommended storage conditions for IMP packs are:

- Below 25°C
- Store in original packaging to protect from light

All IMP packs should be stored in a designated, secure area within the neonatal unit to enable recruitment and dosing at any time of day.

It is recommended that IMP packs be stored in the routine medication storage area of the neonatal unit, therefore providing restrictive access. However, IMP packs must be kept clearly segregated to avoid any potential confusion with standard medicine stock.

Alternative storage locations are acceptable, provided they meet the following conditions:

- The storage is secure and access-controlled
- IMP packs can be readily accessed to support timely recruitment

9. Temperature monitoring and management of excursions

In accordance to the SmPC, dexmedeTOMIDine ampoules do not require any special temperature storage conditions. For the sodium chloride 0.9% placebo ampoules, thermal stability data supports heat sterilisation at 121°C for 15 minutes. Therefore, applying a risk-proportionate approach, no additional temperature monitoring is required specifically for the trial, provided that IMP packs are stored within the routine medication storage area of the neonatal unit where routine temperature monitoring is expected to be in place.

Excursion reporting to the CTU is required only when a temperature excursion affects the entire medication storage area and local assessment has concluded that all medicines are affected.

10. Randomisation

Eligible babies will be randomised using REDCap, a secure, web-based randomisation system available 24 hours a day. A confirmation email will be sent to the randomising clinician, local principal investigator (PI), the named research nurse, and any additional relevant personnel, providing the allocated treatment as a unique Pack ID to maintain blinding.

11. IMP prescribing

The PI, or their delegated prescriber, must prescribe '**DexmedeTOMIDine or Placebo'** on the baby's prescription chart. The allocated unique **Pack ID** must also be prescribed to enable verification at the point of IMP preparation and administration**.**

12. Dosage of IMP

The IMP must be prescribed as an infusion rate in **millilitres per hour (mL/hr)**, based on the baby's **working body weight at the start of the infusion**. The working body weight should have been reviewed within the last 7 days. This weight should be used throughout the treatment period irrespective of any changes in the baby's actual or working weight.

Pre-defined infusion rates based on body weight are provided in Appendix C. For the first 24 hours, the infusion is given at half the target rate. After 24 hours, the infusion rate should be increased to full target rate unless it needs adjusting according to the baby's clinical condition as per the titration guide in **Figure 1**. All changes must be prescribed on the baby's prescription chart by the PI or their delegated prescriber.

The maximum duration of IMP treatment is 120 hours from the start of infusion. The IMP must be discontinued at 120 hours. If the baby still requires analgesia after this time, morphine or other analgesics should be prescribed and administered according to routine clinical practice.

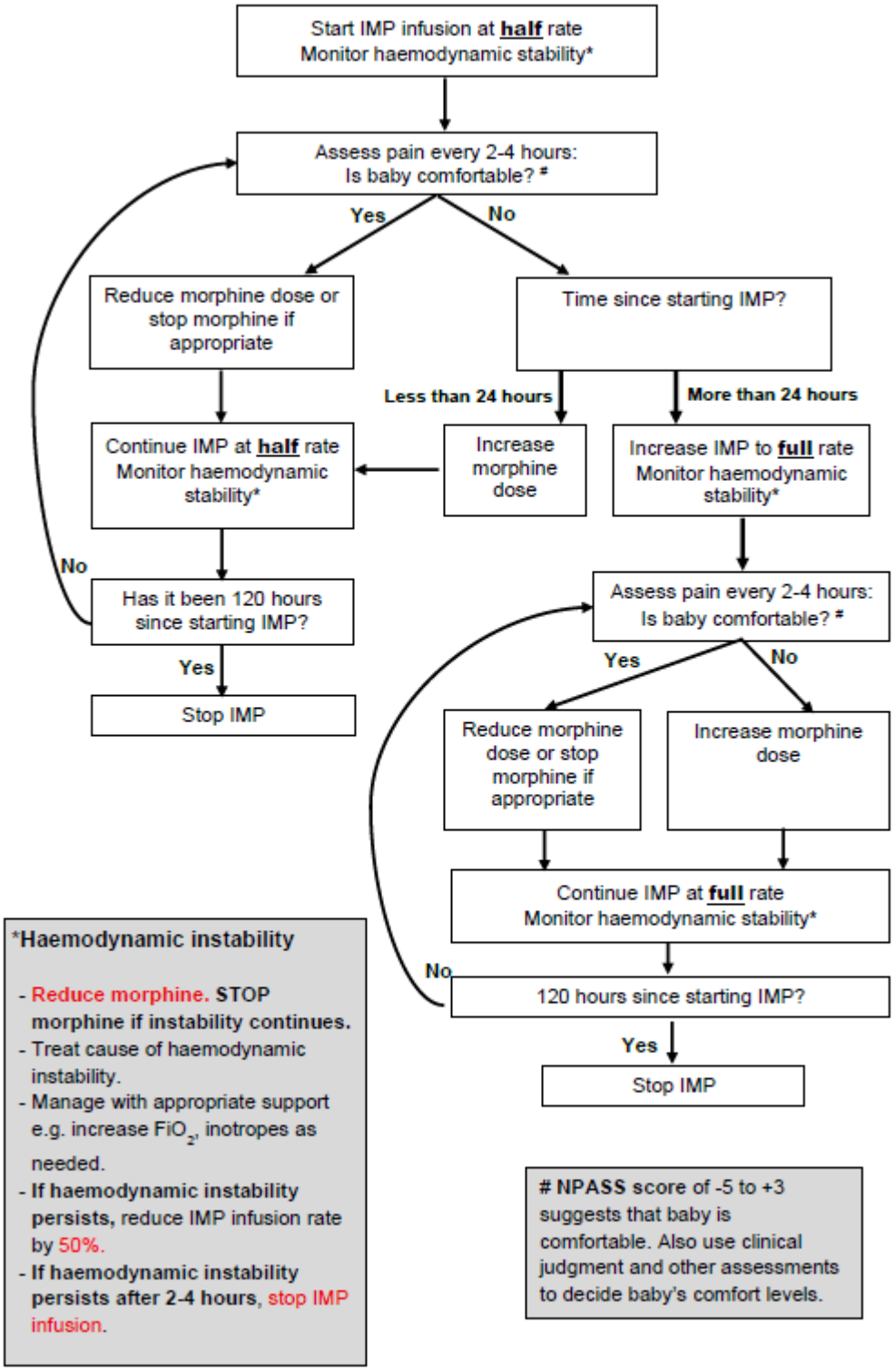
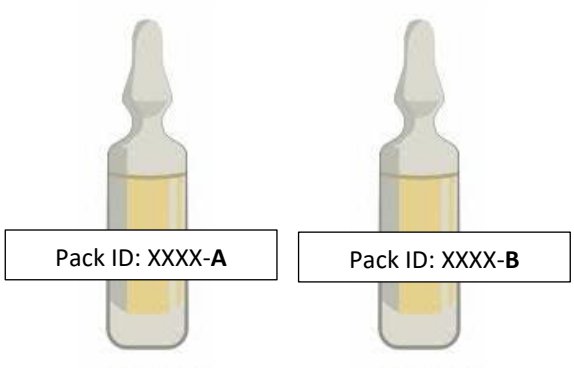


Figure 1. IMP infusion rate and morphine dose modifications

13. Preparation of IMP

1. Verify that the prescribed Pack ID on the baby's prescription chart matches the randomisation confirmation for the baby.
2. According to the Pack ID allocated for the baby, locate the IMP pack and complete the outer box label with the baby's details. Each IMP pack contains 7 ampoule pairs, sufficient for the full 120-hour treatment period.
3. Prepare a new infusion syringe every 24 hours, or earlier if clinically required.
4. Remove one ampoule pair from the allocated IMP pack. **Each pair consists of two ampoules: one labelled with the suffix 'A' and the other with 'B'; both ampoules in the pair must be used for preparation. Do not mix ampoules from different pairs.**



5. Verify that the number portion of the Pack ID printed on the ampoules matches the Pack ID on the outer carton.
6. Visually inspect both ampoules for cloudiness, discoloration or particulates. Do not use if the ampoules if damaged or discoloured. If unsuitable, use a new ampoule pair from the same pack.
7. Using aseptic technique, prepare a 50mL infusion syringe according to the baby's working body weight as follows:

For babies with a working body weight of **less than 800 grams**:

- Withdraw **0.25 mL from ampoule A**
- Withdraw **0.25 mL from ampoule B**
- Add **49.5** mL of diluent (Glucose 5% or Sodium Chloride 0.9%)

For babies with a working body weight of **≥ 800 grams**:

- Withdraw **0.5 mL from ampoule A**
- Withdraw **0.5 mL from ampoule B**
- Add **49 mL** of diluent (Glucose 5% or Sodium chloride 0.9%)

8. Label the prepared syringe in accordance with local hospital policy and must include the full name of the IMP '**DexmedeTOMIDine or Placebo'**.
9. The prepared syringe should be used immediately after preparation.
10. Discard used IMP ampoules and empty packaging immediately after preparation in accordance with local clinical waste procedures.

14. Administration of IMP

The IMP must be administered under medical supervision by qualified healthcare personnel. **IMP infusion should be started only after the baby is at least 168 hours (7 completed days) old.**

Where possible, the IMP infusion should be delivered via a dedicated lumen, distinct from the lumen used for bolus or intermittent medication administration.

If only a single lumen is available, the following setup is recommended:

- Reserve an octopus port closest to the patient for bolus or intermittent medications.
- Connect the IMP infusion to a separate port, away from any ports used for critical continuous infusions. (e.g. inotropes or parenteral nutrition)
- In situations where morphine and IMP infusions are administered via the same lumen, do not administer morphine boluses from the continuous morphine infusion syringe. Instead, administer morphine boluses via the designated bolus or intermittent port (see appendix C for example illustration).

Two examples of infusion setup are illustrated in Appendix D, to support local implementation and line safety practices. For information on compatible co-administered medications, refer to the **Y-site compatibility table in Appendix E.**

15. IMP accountability

IMP accountability will be recorded on the Site-Level IMP Accountability Log (Appendix A). In addition, the IMP name, the unique Pack ID, dosage (mL/hr), date and time of administration, and any other relevant administration details must be documented in either the baby's prescription chart or the medical notes.

16. Disposal of IMP

Used IMP ampoules and empty packaging should be discarded after preparation, in accordance with standard clinical practice.

Any unused ampoules remaining after a baby completes treatment must be returned to the pharmacy, recorded on the Site Level IMP Accountability Log (Appendix A), and disposed of locally following documentation.

Expired or unassigned IMP packs must not be destroyed without prior authorisation from the CTU. Once authorised, document on the Site Level IMP Accountability Log (Appendix A), and disposed of locally in accordance with standard clinical practice.

17. Damaged IMP

Any damaged IMP ampoule pair must be documented in the baby's medical notes.

If the remaining ampoules in the assigned IMP pack are insufficient to complete the full treatment course, contact the CTU as soon as possible for further instructions.

18. Drug recall

In the event of a drug recall, the CTU will inform sites and issue appropriate instructions for further action.

19. Emergency unblinding

Refer to protocol section 6.4 for emergency blinding instructions

Appendix A – Site Level Investigational Medicinal Product Accountability Log (Sample)

Site Level investigational Medicinal Product Accountability Log

DEXTA

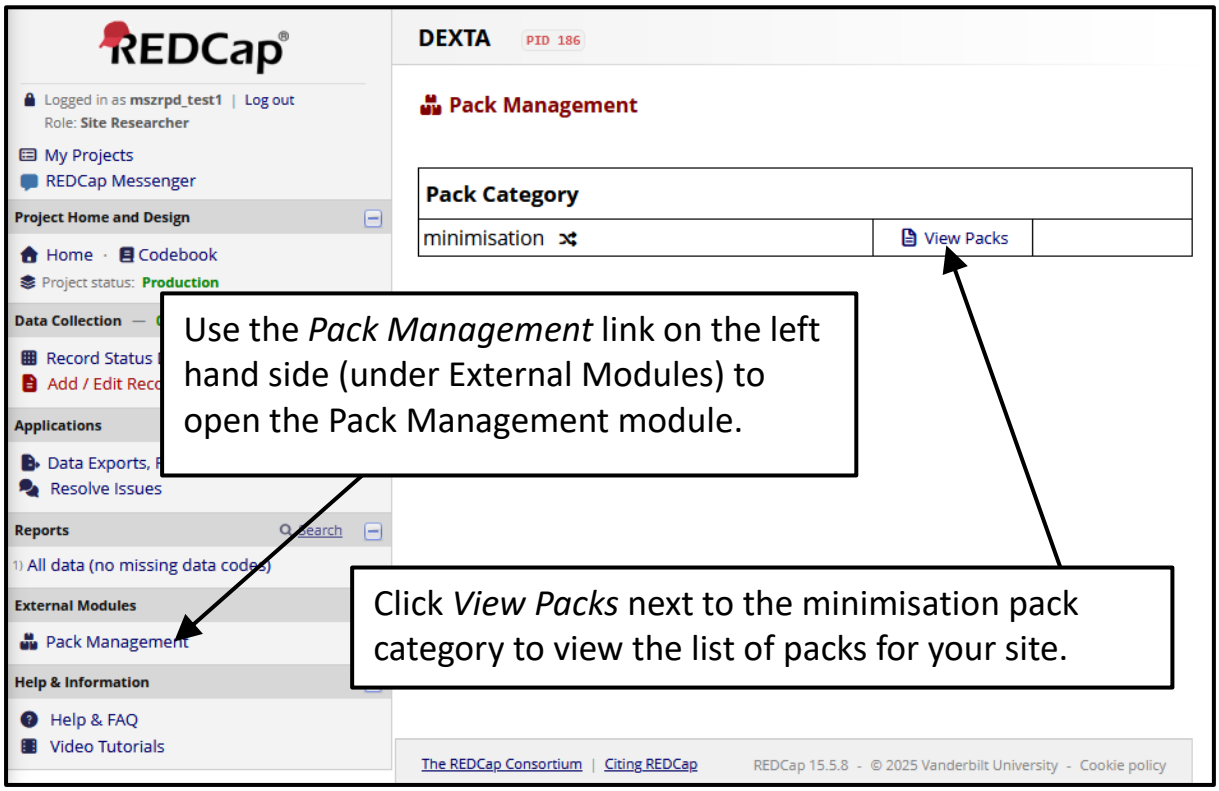
Protocol ID:	DEXTA	**IRAS:**	1012134
Sponsor:	University Hospitals of Derby and Burton NHS Foundation Trust		
IMP description:	DexmedeTOMIDine 100 micrograms/mL or Placebo concentrate for solution for Infusion		
Pack size:	7 pairs of 2mL ampoules	**Storage:**	Protect from light. Store below 25°C.
Batch number:		**Expiry date:**	
Site name:		**Principal investigator:**	

Received by			Transferred to Neonatal Unit			Receipt confirmation	Disposal at site	
Pack ID	**Date & Time received**	**Received by (Initials)**	**Date & Time received**	**Transferred by (Initials)**	**Received by (Initials)**	**Confirmed receipt on REDCap after transfer (Initials and date)**	**Quantity**	**Disposed by (Initials)**

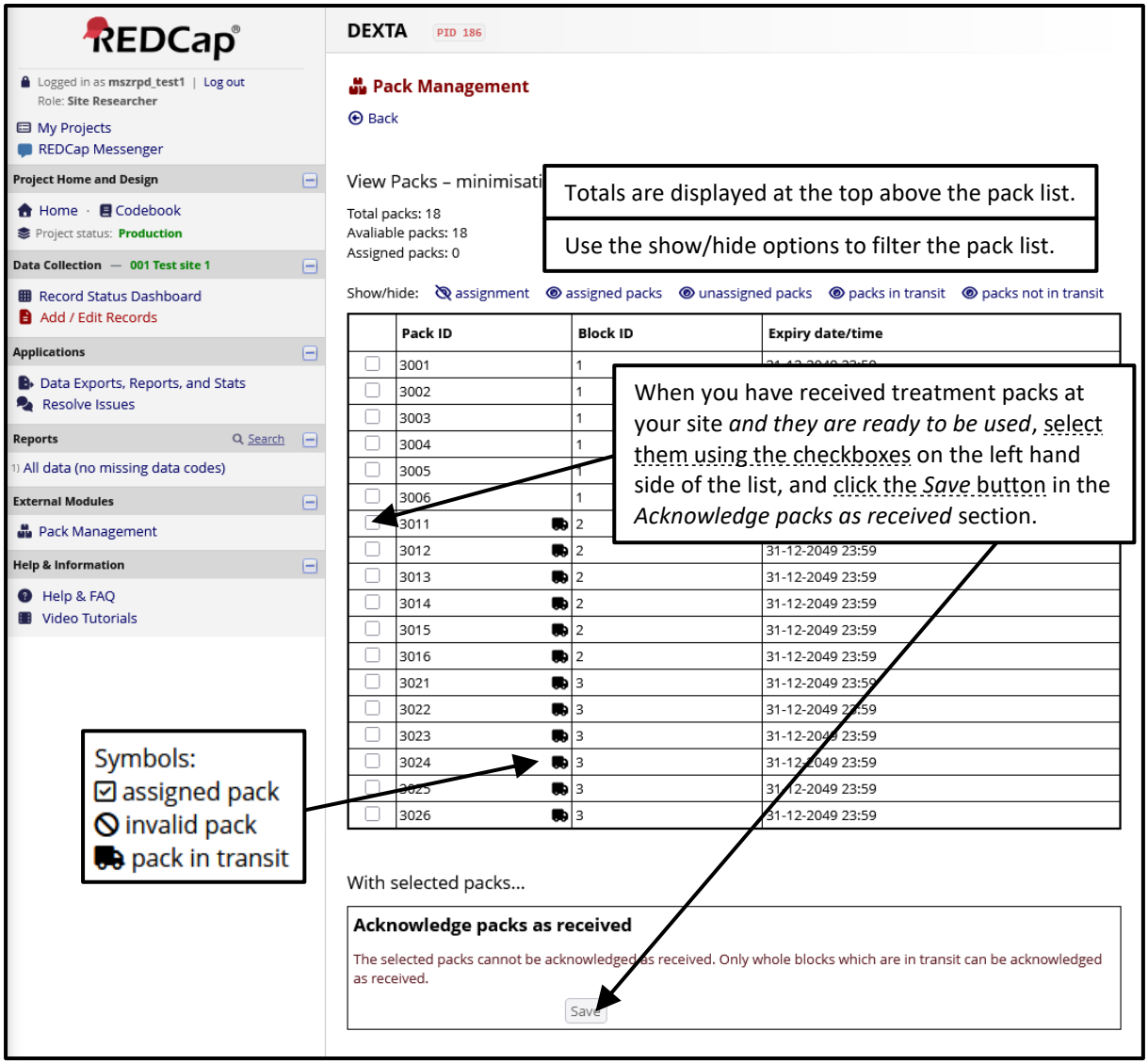
Version 1 Dated: 03 Oct 2025

Appendix B – REDCap instructions for the Pack Management System

After logging in to REDCap and navigating to the DEXTA project, you will see a link on the left-hand side for *Pack Management*. When you click this link, you will see a page with a link to *View Packs*, as shown below.



- Click *View Packs*, a list of the packs that have been issued to your site will appear.
- When new IMP packs are issued to your site, they will appear in this list as in transit (denoted with a van symbol) and these packs will not be used for randomisation until someone has *Acknowledged packs as received*.
- **Only acknowledge IMP packs as received once they are available on the neonatal unit.**
- Using the checkboxes on the left-hand side of the list to select the relevant Pack ID received.
- In the *Acknowledge packs as received* section, click *Save* button to confirm receipt.
- If there is a damaged IMP pack, contact the CTU by emailing dexta@nottingham.ac.uk with the details who will be able to mark the pack as invalid.


REDCap
Logged in as mszrpd_test1 | Log out
Role: Site Researcher
My Projects
REDCap Messenger
Project Home and Design
Home · Codebook
Project status: Production
Data Collection — 001 Test site 1
Record Status Dashboard
Add / Edit Records
Applications
Data Exports, Reports, and Stats
Resolve Issues
Reports
Search
1) All data (no missing data codes)
External Modules
Pack Management
Help & Information
Help & FAQ
Video Tutorials
DEXTA
PID 186
Pack Management
Back
View Packs – minimisati
Total packs: 18
Avaliable packs: 18
Assigned packs: 0
Totals are displayed at the top above the pack list.
Use the show/hide options to filter the pack list.
Show/hide: assignment assigned packs unassigned packs packs in transit packs not in transit
Pack ID
Block ID
Expiry date/time
3001 1
3002 1
3003 1
3004 1
3005 1
3006 1
3011 2 31-12-2049 23:59
3012 2 31-12-2049 23:59
3013 2 31-12-2049 23:59
3014 2 31-12-2049 23:59
3015 2 31-12-2049 23:59
3016 2 31-12-2049 23:59
3021 3 31-12-2049 23:59
3022 3 31-12-2049 23:59
3023 3 31-12-2049 23:59
3024 3 31-12-2049 23:59
3025 3 31-12-2049 23:59
3026 3 31-12-2049 23:59
When you have received treatment packs at your site and they are ready to be used, select them using the checkboxes on the left hand side of the list, and click the Save button in the Acknowledge packs as received section.
Symbols:
assigned pack
invalid pack
pack in transit
With selected packs...
Acknowledge packs as received
The selected packs cannot be acknowledged as received. Only whole blocks which are in transit can be acknowledged as received.
Save

Appendix C – Infusion rate

Infusion rate for babies with working body weight less than 800 grams

Preparation: 0.25mL Ampoule A + 0.25mL Ampoule B + 49.5mL diluent

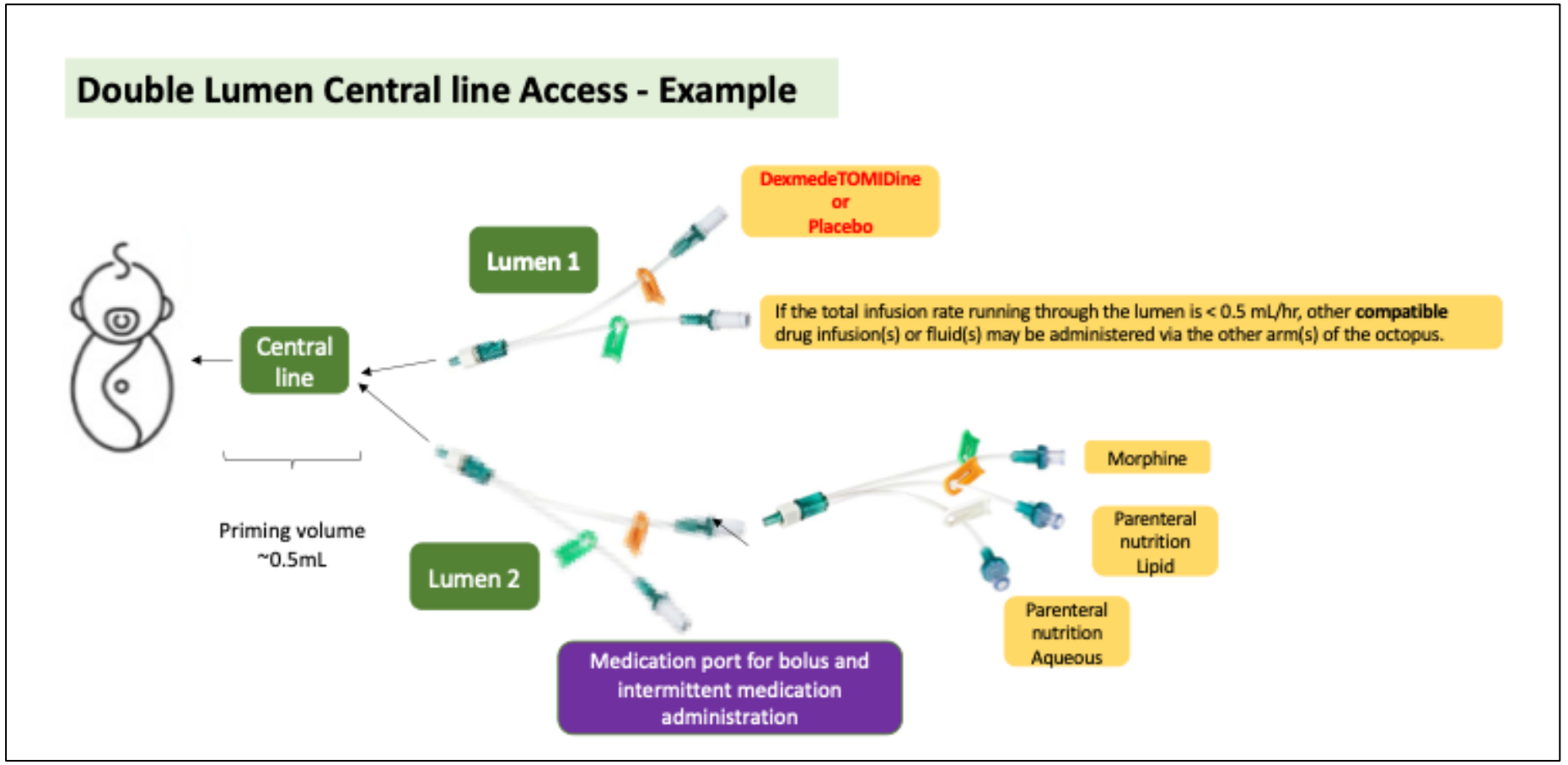
Body weight	Half rate (mL/hr)	Full rate (mL/hr)
450 - 469 grams	0.11	0.23
470 - 489 grams	0.12	0.24
490 - 509 grams	0.12	0.25
510 - 529 grams	0.13	0.26
530 - 549 grams	0.13	0.27
550 - 569 grams	0.14	0.28
570 - 589 grams	0.14	0.29
590 - 609 grams	0.15	0.30
610 - 629 grams	0.15	0.31
630 - 649 grams	0.16	0.32
650 - 669 grams	0.16	0.33
670 - 689 grams	0.17	0.34
690 - 709 grams	0.17	0.35
710 - 729 grams	0.18	0.36
730 - 749 grams	0.18	0.37
750 - 769 grams	0.19	0.38
770 - 789 grams	0.19	0.39
790 - 799 grams	0.20	0.40

Infusion rate for babies with working body weight ≥ 800 grams

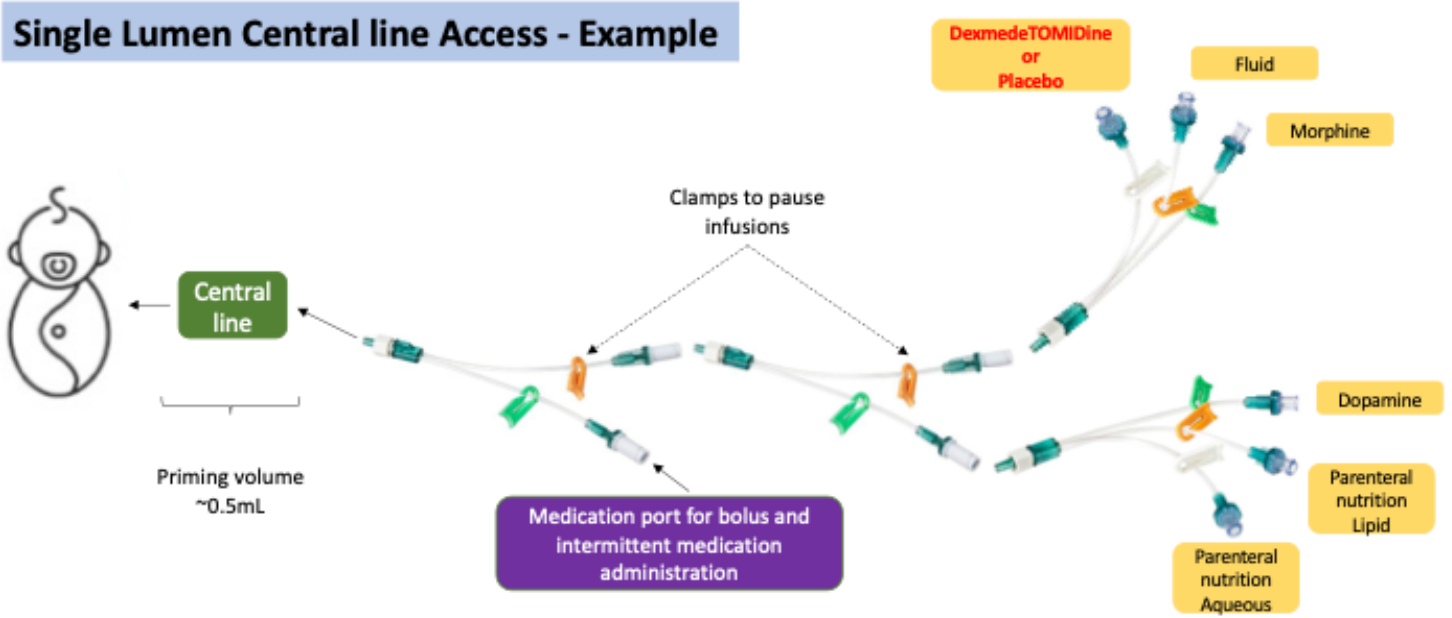
Preparation: 0.5mL Ampoule A + 0.5mL Ampoule B + 49mL diluent

Body weight	Half rate (mL/hr)	Full rate (mL/hr)
800 - 849 grams	0.10	0.20
850 - 899 grams	0.11	0.21
900 - 949 grams	0.11	0.23
950 - 999 grams	0.12	0.24
1 - 1.09 kg	0.13	0.25
1.1 - 1.19 kg	0.14	0.28
1.2 - 1.29 kg	0.15	0.30
1.3 - 1.39 kg	0.16	0.33
1.4 - 1.49 kg	0.18	0.35
1.5 - 1.59 kg	0.19	0.38
1.6 - 1.69 kg	0.20	0.40
1.7 - 1.79 kg	0.21	0.43
1.8 - 1.89 kg	0.23	0.45
1.9 - 1.99 kg	0.24	0.48
2 - 2.09 kg	0.25	0.50
2.1 - 2.19 kg	0.26	0.53
2.2 - 2.29 kg	0.28	0.55
2.3 - 2.39 kg	0.29	0.58
2.4 - 2.49 kg	0.30	0.60
2.5 - 2.59 kg	0.31	0.63
2.6 - 2.69 kg	0.33	0.65
2.7 - 2.79 kg	0.34	0.68
2.8 - 2.89 kg	0.35	0.70
2.9 - 2.99 kg	0.36	0.73
3 - 3.09 kg	0.38	0.75
3.1 - 3.19 kg	0.39	0.78
3.2 - 3.29 kg	0.40	0.80
3.3 - 3.39 kg	0.41	0.83
3.4 - 3.49 kg	0.43	0.85
3.5 - 3.59 kg	0.44	0.88
3.6 - 3.69 kg	0.45	0.90
3.7 - 3.79 kg	0.46	0.93
3.8 - 3.89 kg	0.48	0.95
3.9 - 3.99 kg	0.49	0.98

Appendix D – Administration information



Single Lumen Central line Access - Example



Bolus medications
- Clamp and pause all infusions.
- Flush the medication port.
- Administer the medication via the medication port.
- Flush the medication port.
- Unclamp and resume all infusions.

Medications by intermittent infusions
- Clamp and pause all infusions.
- Flush the medication port.
- Start intermittent infusion via the medication port.
- **Clamp off the octopus with** DexmedeTOMIDINE/Placebo.
- **Resume** all other **compatible** critical continuous infusions.
- When intermittent infusion is complete, clamp and pause all infusions.
- Flush the medication port.
- Unclamp and resume all infusions.

Appendix E – DexmedeTOMIDine hydrochloride Y-site compatibility

Exclusion from this list does not imply compatibility

Drug	Y-site compatibility	Reference / Additional notes
Adrenaline	✓	2,3,4
Amikacin sulfate	✓	4
Amphotericin B	×	2,4
Atracurium besylate	✓	1,2,3,4
Caffeine citrate	No Information	-
Calcium gluconate	✓	2,3,4
Cefotaxime sodium	✓	4
Cefuroxime sodium	✓	4
Co-trimoxazole	✓	2,3,4
Dexamethasone (base / phosphate)	✓	2,4
Diazepam	×	2,4
Dinoprostone	No Information	-
Dobutamine hydrochloride	✓	1,2,3,4
Dopamine hydrochloride	✓	1,2,3,4
Erythromycin lactobionate	✓	4
Fat emulsion, intravenous	?	Separate infusion preferred
Fluconazole	✓	2,4
Furosemide	✓	2,3,4
Gentamicin sulfate	✓	2,3,4
Glucose 5%	✓	1,2,3
Heparin sodium (unfractionated)	✓	2,3,4
Hydrocortisone sodium succinate	✓	2,4
Insulin	No Information	-
Ketamine hydrochloride	×	4
Levetiracetam	✓	4
Magnesium sulfate	✓	2,3,4
Meropenem	✓	4
Metronidazole	✓	2,3,4
Midazolam hydrochloride	✓	1,2,3,4
Milrinone lactate	✓	2,3,4
Morphine sulfate	✓	1,2,3,4
Noradrenaline bitartrate	✓	1,2,3,4

Exclusion from this list does not imply compatibility

Drug	Y-site compatibility	Reference / Additional notes
Paracetamol	No Information	-
Piperacillin sodium–tazobactam sodium	✓	4
Potassium chloride	✓	2,3,4
Propofol	✓	2,3,4
Rocuronium bromide	✓	1,2,3
Sildenafil	No Information	-
Sodium bicarbonate	?	Separate infusion preferred
Sodium chloride 0.9%	✓	1,2,3
Succinylcholine chloride	✓	1,4
Thiopental sodium	✓	1,2,3
Tobramycin sulfate	✓	2,4
Total Parenteral Nutrition (TPN)	?	Separate infusion preferred
Vancomycin hydrochloride	✓	2,3,4
Vecuronium bromide	✓	1,2,3,4

References:

1. Summary of Product Characteristics (Brand: Orion Pharma, AS Kalceks, B.Braun)
2. Medusa (Version 3)
3. Thames Valley Y-site IV Compatibility chart (September 2015)
4. ASHP Injectable Drug Information