SOP - Handling study medication DOXA-trial

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1. INTRODUCTION

This document describes the Standard Operating Procedure on Handling of study medication for the DOXA-trial (MEC-2020-0078).

Aim: The main objective of the DOXA-trial is to study if doxapram is safe and effective in reducing the composite outcome death and neurodevelopmental impairment at 2 years corrected age.

Study design: Randomized, double blinded placebo-controlled trial, stratified for center and gestational age before or after 26 weeks at birth. Block randomization will be used.

Study population: 398 newborn infants admitted to the Neonatal Intensive Care unit, with a gestational age of less than 29 weeks at birth with optimal non-invasive respiratory support (nCPAP or nIPPV) and caffeine treatment that still show apnea.

Study medication:

- Polypropylene 50 ml vial
- Verum: Doxapram HCl 2 mg/ml in glucose 5%
- Placebo: Glucose 5%
- Volume: Volume per vial of 50 ml
- 1 kit contains 10 vials study medication
- Size of 1 kit is: length x width x depth = 93 x 93 x 223 mm

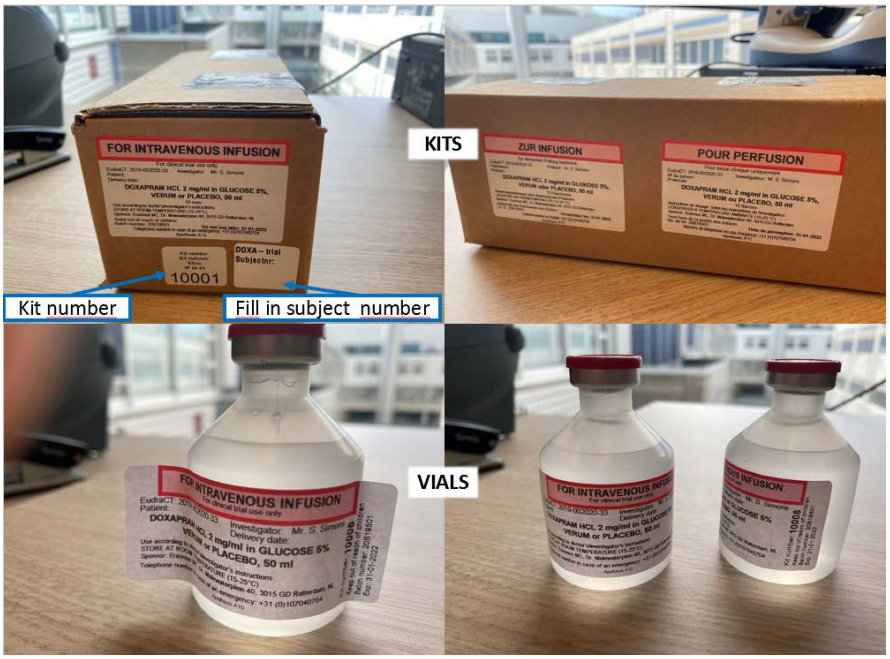

Figure 1. The kits, vials and the labels.

2. CENTRAL STORAGE OF STUDY MEDICATION

Manufacturing of study medication 5000 vials doxapram and 5000 vials placebo by the Apotheek A15 takes place in 3 batches of 1667 vials each. After release of a batch from the manufacturer, central storage of study medication takes place in the Pharmacy of the Erasmus MC in Rotterdam.

Conditions are permanently monitored with respect to temperature.

Storage conditions should remain within 15-27 degrees Celsius. Nevertheless, the temperature may increase up to 30 degrees with the limitation that the cumulative time of the temperature between 27 and 30 degrees does not exceed 60 days.

3. CENTRAL DISTRIBUTION OF STUDY MEDICATION TO EACH SITE

Study medication is distributed 1 or 2 times per year to each participating site from the pharmacy of the Erasmus MC Rotterdam if the remaining number of kits in the pharmacy on site is below the minimum for each specific site which is agreed depending upon the expected inclusion rate.

Study medication will be transported by Post NL from the hospital pharmacy of the Erasmus MC Rotterdam to the local hospital pharmacy of each site.

4. RECEIPT AND LOCAL STORAGE OF STUDY MEDICATION

Upon reception of the study medication by the Local Hospital Pharmacy the accountability should be updated, both on paper and in ALEA (SOP ALEA instructions). For the Belgium sites a different logistic route may be agreed on; e.g. an immediate dispense of the study medication to the NICU and no storage in the pharmacy. Each Local Hospital Pharmacy has an ALEA account.

5. RANDOMISATION AND NEW KIT ALLOCATION

ALEA is the software program that is used for double blind randomization of subjects to the verum- or placebo-arm. The SOP ‘ALEA instructions’ describes the steps how to randomize. After randomization, ALEA will allocate the first kit with 10 vials study medication by supplying a kit number. The subject number needs to be noted at the kit after a kit has been allocated (see Figure 1). When a kit is almost empty, a new kit-number needs to be allocated to the subject in ALEA. This can be done by the local study team and/or by the pharmacy.

6. LOCAL DISPENCING AND STORAGE STUDY MEDICATION

The main stock of study medication will be held in the hospital pharmacy. The local stock of study medication at the NICU-ward or at a pharmacy location close by the ward, needs to hold **accountability of each kit and each vial that is received and used per patient**.

If the number of intact kits at the NICU or at the Ward-Pharmacy are below the agreed minimum (at least 5 kits), new kits should be ordered from the Local Hospital Pharmacy. For Belgium sites without storage of study medication in het hospital pharmacy, a new order from the central pharmacy Erasmus MC in Rotterdam should take place. The request for dispensing new kits from the local hospital

pharmacy stock to the ward as well as from the central pharmacy Erasmus MC should be ordered in ALEA by the steps in the SOP 'ALEA instructions'.

The conditions of the NICU-storage should meet the criteria of **15-27 degrees** Celsius, although the label gives a maximum of 25 degrees Celsius. The manufacturer declared that the preliminary stability data allow to use a maximum temperature of 27 degrees and that the temperature may even increase up to 30 degrees with the limitation that the cumulative time of the temperature between 27 and 30 degrees does not exceed 60 days.

The temperature should be logged at all time, either with active alarm signals or with a periodical readout of the logger (e.g. once per month). If the temperature has exceeded 27 degrees more than 7 days cumulative, please contact Robert Flint or the trial pharmacy of the Erasmus MC.

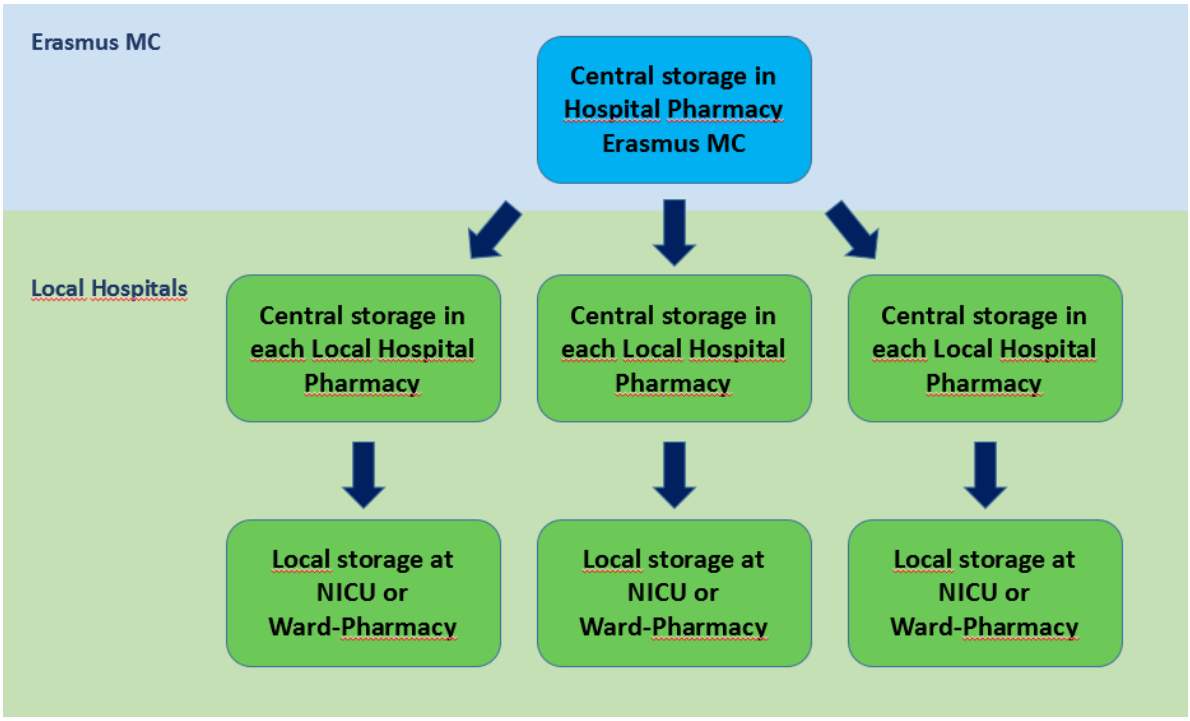

Figure 2. Schematic description of the logistics.

7. PREPARATION OF STUDY MEDICATION

As the vial contains the solution ready to use for administration, preparation of study medication consists of bringing the content of the vial into a syringe and adjust a patient label. The vial study medication **'For intraveneus infusion'** should be used for preparation of the intravenous as well as the (gastro) enteral administration.

8. TRANSFER OF PATIENTS TO NICU IN ANOTHER HOSPITAL

If a randomized patient in the DOXA-trial is transferred from NICU A to NICU B of another hospital, either:

- that is **open** for the DOXA-trial, the patient can remain in the DOXA-trial. The kit that is already allocated to this subject should remain in NICU A and not thrown away (as often the patient will return to NICU A). To change the NICU of the subject in ALEA an email should be send to ict.ctc@erasmusmc.nl with in the cc doxatrial@erasmusmc.nl. ALEA will then choose a next kitnumber from the stock of NICU B. In Castor the location of the subject will be changed to NICU B as well. SAE's and data registration is still required at NICU B.
- that is **not open** for the DOXA-trial, the subject cannot receive DOXA-trial study medication in NICU B. So if open label doxapram has not been administered in NICU B, the subject can remain included for future allocation of DOXA-trial study medication.
  If open label doxapram open label has been administered in NICU B, this subject is not eligible for DOXA-trial study medication anymore.

9. LOSS AND DESTRUCTION OF STUDY MEDICATION

If study medication gets lost, please inform the study team.

Destruction of study medication may be performed by the local hospital pharmacy after approval by the study team in Rotterdam. The initial expiry date will likely be extended, so please contact the study team of the Erasmus MC if the expiry date is near.

10. RECALL OF STUDY MEDICATION

In case of a recall of study medication, ALEA can provide a list to track each kit based on the kitnumber.

11. UNBLINDING

In case unblinding is required please follow the SOP 'Emergency unblinding'.

12. CONTACT DETAILS

Safety officer: Erasmus MC 0031 (0) 10-7040704

Overall steering team

Sinno Simons	Neonatologist	Erasmus MC	Principal Investigator overall
Jeroen Hutten	Neonatologist	Amsterdam UMC	
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Debbie Nuytemans	Program manager	Neonatology Network Netherlands	
Jarinda Poppe	PhD student	Erasmus MC	
Robert Flint	Hospital pharmacist	Erasmus MC	

For questions regarding this document or study medication, please contact Robert Flint via r.flint@erasmusmc.nl

13. APPENDICES

Appendix 1: ALEA instructions

Appendix 2: SOP Emergency unblinding