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EUROPAIN (EUROpean Pain Audit In Neonates)

European survey of sedation and analgesia practices for newborns admitted to intensive care units

Nederlandse Versie: *V1*

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NEDERLANDSE SAMENVATTING VAN DE EUROPESE STUDIE

1.1 ACHTERGROND EN RATIONALE

Het behandelen en verlichten van pijn is een fundamenteel mensenrecht, ongeacht leeftijd. Pasgeborenen kunnen pijn voelen, waarbij te vroeg geboren pasgeborenen nog gevoeliger zijn voor pijn dan voldragen pasgeborenen. Juist de meest kwetsbare prematuur geboren neonaten worden blootgesteld aan de meeste pijn.
Pasgeborenen opgenomen op de intensive care (neonatale intensive care unit (NICU) en pediatrische intensive care unit (PICU)), moeten tijdens hun verblijf tientallen of zelfs honderden pijnlijke procedures ondergaan. Voor veel van de op een NICU opgenomen pasgeborenen bestaan deze pijnlijke procedures onder andere uit endotracheale intubatie, gevolgd door mechanische ventilatie. Ter behandeling van de pijn en de stress (gerelateerd zijn aan deze beademing, pijnlijke procedures of pijn gerelateerd aan onderliggende ziekten) worden sedativa en analgetica gebruikt bij pasgeborenen opgenomen op de intensive care units. Het meten van de mate van pijn bij pasgeborenen is echter moeilijk en subjectief. Hierdoor bestaat er veel variatie en een breed scala aan manieren waarop pijnstilling en sedatie bij pasgeborenen worden gegeven. Tot op heden is er nauwelijks onderzoek verricht naar de manier waarop analgesie en sedatie op verschillende intensive care afdelingen worden gewaarborgd

Waarom is sedatie en pijnstilling nodig?
Kunstmatige beademing is een potentieel pijnlijke interventie. Volwassenen beschrijven beademing vaak als een pijnlijke en angstige ervaring. Het belangrijkste doel van sedatie en analgesie zijn: vermindering van pijn, stress en prikkelbaarheid, het bevorderen van stabiele bloeddruk, de bevordering van oxygenatie en synchronisatie van beademing. Vermindering van stress, maar ook minder schommelingen in bloeddruk en oxygenatie verlagen de lange termijn risico's op neurologische letsel en overlijden.
Pijn en stress tijdens de neonatale periode kan schadelijk zijn op korte en lange termijn. Middels adequate pijnstilling kunnen sommige van deze gevolgen worden verminderd. Onderzoek toont aan dat adequate sedatie en pijnstilling noodzakelijk is in beademde pasgeborenen.

Internationale Statements die pijnstilling en sedatie aanbevelen
Het toegenomen besef dat pasgeborenen pijn kunnen voelen, de ethische verplichting om deze pijn te behandelen en het toenemende bewijs dat onbehandelde neonatale pijn leidt tot een veranderde reactie op pijnprikkels tot in de kindertijd, hebben geleid tot de ontwikkeling van internationale en nationale richtlijnen voor het gebruik van analgetica in de neonatale populatie.
Deze richtlijnen verklaren dat neonatologie afdelingen protocollen moeten ontwikkelen en implementeren voor pijnstilling en sedatie. De beschikbare literatuur is echter nog tegenstrijdig over het gebruik van sedatie en analgesie voor geventileerde neonaten. Er is onvoldoende bewijs voor het routinematig gebruik van opioïden in beademde pasgeborenen en opioïden dienen gebruikt te worden op

basis van de behoefte van de individuele patient. Sedatie en analgesie bij niet beademde pasgeborenen is uiterst zeldzaam.

Praktijk in Europa en VS

Gegevens over het gebruik van sedatie en analgesie in de praktijk bij beademde neonaten zijn zeer zeldzaam. In 1995 toonde een in de Verenigde Staten uitgevoerd onderzoek (SOPAIN) dat bepaalde factoren het gebruik van continue pijnstilling bij pasgeborenen voorspellen: kunstmatige beademing, hogere zwangerschapsduur en mannelijke geslacht.
In 2005 toonde de Franse EPIPPAIN studie aan dat 69,6% van de beademende pasgeborenen continue sedatie en analgesie kreeg. Hierbij viel een enorme variatie op tussen centra van 16,7% naar 90,9%. De meest gebruikte medicijnen waren midazolam en morfine.
Tot op heden zijn er geen gegevens beschikbaar die vergelijking van neonatale pijn behandeling tussen Europese landen mogelijk maken. Deze gegevens maken een onderlinge vergelijking van de praktijken met state-of-the-art kennis mogelijk.

Studie hypothese

De EUROPAIN studie is een epidemiologische studie die gebaseerd is op de volgende hypothese:

- De meeste beademde pasgeborenen krijgen continue sedatie en pijnstilling
- Niet beademde pasgeborenen krijgen geen sedatie
- Morfine, fentanyl en midazolam zijn de meest gebruikte medicamenten in deze setting.
- Gevalideerde pijn scores om de mate van pijnstilling en sedatie te controleren worden nauwelijks gebruikt.
- De meeste afdelingen hebben een sedatie en pijnstillings protocol voor beademde neonaten, maar er bestaan grote verschillen tussen individuele behandelaars, tussen verschillende afdelingen in hetzelfde land en tussen verschillende Europese landen.
- Ontwikkeling, verspreiding, en een regelmatige update van gemeenschappelijke Europese normen zal de zorg en de klinische resultaten van beademde pasgeborenen verbeteren.

1.2 HOOFD DOELSTELLING

- Het vaststellen van de huidige dagelijkse praktijk met betrekking tot het gebruik van analgetica en sedativa bij beademde pasgeborenen in verschillende Europese landen.

1.3 BELANGRIJKSTE UITKOMSTEN

- Het aantal beademde pasgeborenen dat sedatie en pijnstilling krijgt in verschillende Europese afdelingen
- Het soort medicatie dat gebruikt wordt voor pijnstilling en sedatie bij beademde pasgeborenen in Europa
- De lengte van medicatie gebruik voor pijnstilling en sedatie bij beademde pasgeborenen.
- Overeenkomsten en verschillen van sedatie en analgesie gebruik tussen Europese landen

1.4 SECUNDAIRE DOELEN EN UITKOMSTEN

- Het vaststellen van de proportie neonatale afdelingen die een lokaal geschreven protocol hebben gemaakt en geïmplementeerd waarin continue sedatie en pijnstilling voor beademde pasgeborenen en voor procedurele pijn wordt gegeven.
- Het documenteren van gepubliceerde richtlijnen voor neonatale pijnstilling en sedatie in verschillende Europese landen en het verkrijgen van consensus over een Europese standaard die in alle medische settings gebruikt kan worden.
- Het vaststellen in hoeverre pijnscores bij beademde pasgeborenen worden gebruikt en evaluatie van de invloed hiervan op het gebruik van pijnstilling.
- Het vaststellen in hoeverre ontwenningsymptomen worden beoordeeld en voorkomen.

Secondaire uitkomsten

- Variatie tussen Europese landen in de proportie van het aantal afdelingen dat een lokaal geschreven richtlijn heeft ontwikkeld en geïmplementeerd voor sedatie en analgesie bij beademde pasgeborenen.
- Identificatie en beschrijving van nationale sedatie en pijnstillingsrichtlijnen in alle deelnemende landen. Identificatie van aanbevolen medicatie.

1.5 DESIGN

- Epidemiologische observationele studie.

1.6 Studie plan

De EUROPAIN studie is een observationele studie die daarom niet interfereert met de dagelijkse zorg op de afdelingen. Deelname aan de studie leidt tot geen enkele verandering in behandeling of toegenomen belasting voor de patiënt. Deze observationele studie zal alleen epidemiologische data verzamelen over de dagelijkse praktijk op de afdeling.

De inclusiecriteria zijn:

- Alle pasgeborenen tot een gecorrigeerde post conceptuele leeftijd van 44 weken. Dit betekent bijvoorbeeld dat een neonaat met een zwangerschapsduur van 40 weken geïncludeerd kan worden tot 28 dagen (4 weken) na de geboorte (post nataal). Een pasgeborene die na 32 weken zwangerschap wordt geboren kan tot 12 weken na de geboorte worden geïncludeerd.

Op de afdeling

- Er worden geen aanpassingen aan de huidige behandelingsprotocollen gedaan door deelname aan de EUROPAIN studie. De afdelingscoördinator zal alleen data aanleveren over de lokale protocollen voor de behandeling van pijn en sedatie en algemene data over de afdelingsstatistieken. Elke behandeling is toegestaan voor geïncludeerd patiënten omdat deze studie niet uit een interventie bestaat.
- Een verpleegkundige, een arts en een data manager zullen per afdeling worden aangewezen.

Op national niveau

- De landelijke coördinator zal data aanleveren met betrekking tot nationale richtlijnen ter behandeling en preventie van procedurele en continue pijn bij pasgeborenen.

Data verzameling

- De duur van data verzameling voor elk geïncludeerd kind is 28 dagen. De data verzameling stopt echter eerder indien de patiënt de afdeling verlaat (ontslag, overplaatsing naar een andere afdeling, overlijden).
- Data zullen verzameld worden op individuele data verzamelformulieren. Deze formulieren bevatten demografische gegevens, ademhalingsondersteuning, continue of intermitterende sedativa, analgetica en spierverslappers, pijnscores en data over ontwenningsverschijnselen.
- Papieren data verzamelformulieren zijn geschreven in het Engels met daarbij Nederlandse vertalingen. De web-based databases bevatten Nederlandse vragenlijsten.
- De data verzamelformulieren zullen worden ingevuld door de afdelingsverpleegkundige of arts of een door hen aangewezen persoon.
- Voor elk centrum zullen gedurende 1 maand patiënten worden geïncludeerd.
- Data zullen worden ingevoerd via een beveiligde web-based vragenlijst.

1.7 Onderbouwing van het aantal patiënten

Bij de bepaling van het aantal te includeren neonaten om mogelijke verschillen in sedatie en pijnstillingsgebruik tussen verschillende deelnemende Europese landen vast te stellen hebben we rekening gehouden met een scenario waarbij de verschillen klein zijn. Daarom kozen we een effect size (W) van 0.1. Daarnaast hebben we aangenomen dat 15 landen zullen deelnemen. Met behulp van NCSS-PASS 2008 software stelden we vast dat een sample size van 2303 pasgeborenen een power van 90% bereikt bij een effect size (W) van 0.1 met 14 vrijheidsgraden (15 centra) in een Chi-Square test met een significantie niveau (alfa) van 0.05. Daarom is het doel 154 pasgeborenen per centrum te includeren.

1.8 Hoofd activiteiten tijdens de studie

- In elk land zal de Nationale Principal Investigator (NPI) uitnodigingen sturen naar alle level 3 neonatale afdelingen van het land om deel te nemen aan de

studie. De NPI zal de namen, emailadressen en telefoonnummers van de afdelingen die toestemming geven voor deelname doorgeven aan de hoofdonderzoekers van de EUROPAIN studie.

- De NPI is verantwoordelijk voor de coördinatie van alle afdelingen in het betreffende land en zorgt voor communicatie met de hoofdonderzoekers van de EUROPAIN studie.
- De NPI zal demografische gegevens over het deelnemende land verzamelen.
- Een verpleegkundige, een arts en een datamanager zal per afdeling worden aangewezen. De coördinerende verpleegkundige en arts zijn verantwoordelijk voor het informeren van alle afdelingsstaf over de studie.
- De EUROPAIN studie hoofdonderzoekers hebben een specifieke web-based database gemaakt waarin data kunnen worden verzameld. Data kunnen direct worden ingevoerd vanaf een patiëntenformulier. Een papieren kopie van de database zal worden rondgestuurd zodat centra die dat willen data errst op papier kunnen invoeren. De medisch coordinator of iemand die door hem (haar) is aangewezen zal de data invoeren in deze special ontworpen databases.
- De coördinerende arts zal algemene statistieken van de afdeling zoals aantal bedden, aantal opnames, jaarlijkse beademingsdagen, etc doorgeven aan de hoofdonderzoekers van de EUROPAIN studie.
- Elke afdeling zal daarnaast doorgeven welke lokale protocollen aanwezig zijn voor sedatie en pijnstilling van beademende neonaten op de afdeling, inclusief gebruikelijke behandeling van ontwenning en het gebruik van pijnscores.
- MONITORING PANEL. Er zal een ‘monitoring panel’ worden ingesteld dat de vorderingen van de studie zal vervolgen. Dit panel draagt zorg voor communicatie met alle deelnemende centra. Het ‘monitoring panel’ zal bestaan uit 2 full-time aangestelde personen gedurende de studie periode. Zij zullen worden gestationeerd in Parijs en zullen werken onder de verantwoordelijkheid van de EUROPAIN studie hoofdonderzoekers.

1.9 Verwachte resultaten en potentiële implicaties

Volgens onze werkhypothese verwachten we te vinden dat de meeste beademde pasgeborenen op Europese afdelingen continue sedatie en analgesie zullen krijgen. Daarbij denken we echter dat er enorme verschillen binnen landen en tussen landen zullen bestaan. Deze verschillen zullen zeer waarschijnlijk ook bestaan in de ontwikkeling van lokale geschreven protocollen. Deze studie zal daarnaast ook de verschillen in het gebruik van verschillende analgetica en sedativa bij beademde neonaten duidelijk maken. Op dit moment zijn deze gegevens niet beschikbaar.
Het neonatale netwerk dat door de EUROPAIN studie zal worden gecreëerd en de resultaten die via dit netwerk zullen worden verspreid zullen de behandeling van pijn bij pasgeborenen in Europa sterk verbeteren. De beschikbaarheid van deze data maakt het mogelijk de praktijken te vergelijken met state-of-the-art kennis.

2 BACKGROUND AND RATIONALE

2.2 Neonates do feel pain and stress

The alleviation of pain is a basic and human right regardless of age. It has been clearly shown that the neonate is not only able to mount physiological and behavioral responses to pain [1] but also that he (she) is able to express responses at the cortical level when undergoing nociceptive stimulation [2, 3]. These responses are observed even in premature neonates. Furthermore, it has been shown that preterm infants are more vulnerable to pain than more mature infants due to the immaturity of pain modulation systems [4, 5]. The more vulnerable preterm neonates are precisely those that are the more exposed to pain. Neonates admitted to intensive care units, both neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU), undergo dozens or even hundreds of painful procedures during their stay [6-8]. These painful procedures include, for many of the neonates in intensive care, tracheal intubation with mechanical ventilation. The pain and stress that are induced by mechanical ventilation as well as by repetitive procedures or painful diseases has led medical staff to use sedation and analgesia in neonates admitted to intensive care units. The subjectivity and difficulty inherent to pain measurement in neonates have probably contributed to a wide variety of neonatal sedation and analgesia practices. To date, these practices have been rarely studied.

2.3 Why would sedation and analgesia be necessary?

Mechanical ventilation is a potentially painful intervention widely used in NICUs and PICUs. Since neonates demonstrate increased sensitivity to pain, which may affect clinical and neurodevelopmental outcomes, the use of drugs that reduce pain and stress during ventilation must be considered important. The main objectives of sedation and analgesia are: reduction of pain and stress, reduction of irritability, promotion of blood pressure stability, promotion of ventilator synchrony and improvement of oxygenation [9]. In the long term, reduced stress, as well as reduced fluctuations in oxygenation and blood pressure are believed to minimize the risks of neurological injury and death. Since the prevention and treatment of pain are considered a basic human right regardless of age, one may consider that this argument is enough to mandate the use of sedation and analgesia in ventilated neonates. Furthermore, adults often describe mechanical ventilation as a painful [10, 11] and anxiety-provoking [12] experience. However, the use of sedation and analgesia is only conceivable in the respect of the principle that must accompany all medical actions: *first, do no harm*
Premature infants admitted to intensive care units and put on mechanical ventilation show physiological and hormonal stress responses [13]. Barker and Rutter have studied these responses in ventilated preterm infants and found a correlation between the stress responses and illness severity. Among the studied catecholamines, noradrenaline showed the highest correlation with illness severity

with an exponential pattern of increased secretion among infants who subsequently died compared with survivors [13].
Globally, severe stress is deleterious for neonates. Evans et al have shown in a cohort of 146 preterm neonates included in two randomized studies that high serum levels of noradrenalin are associated with higher morbidity and mortality [14]. The immediate impact of severe stress was noted in randomized controlled studies of halothane, morphine, and sufentanil in newborns who had undergone cardiovascular surgery [15].The mortality rate was 27% in those receiving intermittent postoperative analgesia, compared with 0% in those receiving continuous fentanyl or sufentanil therapy. Uncontrolled stress responses produced cardiovascular instability and hypotension, leading to acidosis, disseminated intravascular coagulation, and death. These data strongly indicate that control of surgical stress and pain in neonates can improve morbidity and mortality.

Pain and stress from mechanical ventilation can lead to asynchrony between infant respiration and the ventilator. This asynchrony may cause a forced expiration.
Forced expiratory effort in ventilated neonates may lead to decreases in lung volume and tidal volume, increases in pulmonary resistance, and decreases in lung compliance. Bolivar et al have studied the mechanisms associated with transient episodes of hypoxemia (oxygen saturation <85%) observed in preterm infants undergoing mechanical ventilation [16]. They studied even the episodes that occurred after the acute phase of respiratory failure had passed. They found that all episodes of hypoxemia were preceded by an active exhalation that produced a decrease in end-expiratory lung volume. The reduction in lung volume was immediately followed by a sudden decrease in tidal flow and volume, despite continuation of mechanical ventilation at the same rate and peak pressure. The resulting hypoventilation was associated with a drop in compliance to approximately one half and an increase in resistance to more than double the baseline values. Approximately 30 seconds after the beginning of hypoventilation, the arterial oxygen saturation reached a hypoxemic level (oxygen saturation <85%). They concluded that most hypoxemic episodes were triggered by an expiratory effort that produced a large decrease in lung volume. This reduction in lung volume probably leads to closure of small airways and the development of intrapulmonary shunts, which would explain the rapid development of hypoxemia [16].

In summary, severe pain is a very distressing experience that can increase morbidity and mortality of severely ill neonates [17, 18]. Furthermore, it has been shown that pain and stress experienced during the neonatal period can have deleterious short-term [19, 20] and long-term [21-23] consequences. Some of these consequences have been reduced with adequate analgesic treatment [24, 25]. Current data suggest the necessity to give adequate sedation and analgesia to ventilated neonates.

2.4 Statements promoting the use of sedation and analgesia

The increased awareness that neonates feel pain, the ethical obligation to treat this pain with analgesics, the growing body of evidence demonstrating that untreated neonatal pain can lead to altered reactivity to pain that persists throughout infancy and childhood [26] as well as the need for a humane management of neonates have lead to the development of International and National Guidelines promoting the use

of analgesics in the neonatal population [27, 28]. These Guidelines state that units that provide neonatal care should develop and implement guidelines concerning neonatal pain.

However, the existing literature is still conflicting regarding the use of sedation and analgesia for ventilated neonates. A meta-analysis of several randomized placebo-controlled trials found that ventilated infants given opioids showed reduced pain scores compared to the control group. Mortality, duration of mechanical ventilation, and long and short-term neurodevelopmental outcomes showed no statistically significant differences. The conclusion was that there is insufficient evidence to recommend the routine use of opioids in mechanically ventilated newborns and that opioids should be used selectively [29]. Sedation and analgesia in non ventilated babies is extremely rare.

2.5 Practices across Europe and USA

Some studies regarding sedation and analgesia practices in ventilated neonates have been reported. In the United States, the SOPAIN study group collected data in about 1 068 ventilated and/or postoperative neonates over a one-week-period in 1995 [30, 31] Factors predicting the use of ongoing analgesia and sedation in neonates included: mechanical ventilation, higher gestational age, and male gender. In the French EPIPPAIN study, practices of continuous sedation and analgesia (cSA) were assessed in 303 ventilated newborns in 2006. The rate of cSA was 69.6% with large variations among centers (16.7% to 90.9%). The most frequently used drugs were midazolam and morphine [32].

Practices and policies concerning neonatal pain assessment and pain treatment have been investigated in Austria [33], Austria, Germany and Switzerland [34], France [8, 35], Italy [36], Sweden [37, 38], The Netherlands [6] and Scotland [39]. To date, there are no data permitting the comparison of neonatal pain management within the European countries. The availability of these data will enable comparison of practices with state-of-the-art knowledge.

2.6 Study Hypothesis

The EUROPAIN study is an epidemiological study that is based on the following hypothesis:

- Most newborn ventilated infants receive continuous sedation and analgesia.
- Non ventilated babies are not sedated.
- Morphine, fentanyl and midazolam are the most frequently drugs used in this setting.
- Infrequent use of validated pain assessment tools to monitor sedation and analgesia occurs in ventilated newborn infants.

- Most units have developed written local guidelines for sedation and analgesia in ventilated neonates, but huge variability exists among practitioners in the same unit, across different units in the same country, and across different countries in Europe.

- Development, dissemination, and regular updates of common European standards will improve the care and clinical outcomes of ventilated newborn infants.

3 EUROPAIN STUDY AS PART OF THE NEOOPIOID PROJECT

The EUROPAIN study is part of the NeoOpioid project. NeoOpioid is the acronym for *No pain during infancy by adapting off-patent medicines*, a project coordinated by Karolinska Institutet and supported by the European Community's Seventh Framework Programme under grant agreement No. 223767. EUROPAIN is performed as Work Package # 5, entitled *European survey of sedation and analgesia practices for ventilated newborn infants*.

3.2 General description of the NeoOpioid Project

This project is designed as a comprehensive study aiming to investigate the clinical efficacy and safety effects of opioid therapy in newborns as well as to determine clinical practices across Europe. The NeoOpioid project will advance the science of neonatal pain and stress, the clinical practice of analgesia, the pharmacokinetic determinants, while documenting current therapies and guidelines and developing a new European standard of care for pain relief in its most vulnerable population.

The NeoOpioid project is divided into 6 *Work Packages* (WP), of which EUROPAIN, the present study, is WP 5.

The 6 Work Packages included in the NeoOpioid project are:

1. Management
2. Dose optimization (morphine and fentanyl)
3. Safety and clinical effects (morphine and fentanyl)
4. New child friendly formulation (morphine)
5. European survey – EUROPAIN
6. Administration

3.3 The NeoOpioid consortium

The NeoOpioid project is run by the NeoOpioid Consortium which is coordinated by Karolinska Institutet, Stockholm, Sweden. It is constituted by the following 12 partners (numbers are partner-numbers):

1. Karolinska Institutet (KI), Sweden
2. Uppsala Universitet (UU), Sweden
3. Lunds Universitet (ULUND), Sweden
4. Örebro Universitet (ORU), Sweden
5. Erasmus Universitair Medisch Centrum Rotterdamerasmus MC (EMC), Netherlands
9. EPMC Pharma SPRL (EPMCP), Belgium
10. Helsingin Ja Uudenmaan Sairaanhoitopiirin Kuntayhtyma (HUS), Finland
11 The University of Edinburgh (UEDIN), United Kingdom
12. Assistance Publique-Hôpitaux De Paris (AP-HP), France
13. Universiteit Antwerpen (UA), Belgium
14. Friedrich-Alexander Universitaet Erlangen-Nuernberg (FAU), Germany
15. University of Leicester (ULEIC), United Kingdom.

4 OBJECTIVES OF THE EUROPAIN EPIDEMIOLOGICAL STUDY

4.2 Main objective

- To determine the current clinical practices regarding the use of sedative and analgesic drugs for ventilated newborns in different countries in Europe.

4.3 Principal criteria

- The frequency of ventilated neonates receiving sedation and analgesia in different European units
- The medications used for sedation and analgesia in ventilated neonates across Europe.
- The length of use of medications administered for sedation and analgesia in ventilated neonates
- Similarities and differences in sedation and analgesia practices among european countries

4.4 Secondary objectives

- To determine the proportion of neonatal units that have developed and implemented local written guidelines to provide continuous sedation and

analgesia in ventilated newborn infants as well as to prevent and treat procedural pain.

- To document the published guidelines for neonatal analgesia and sedation in different European countries and develop consensus for common European standards that can be applied in all medical settings.
- To determine the frequency of use of pain assessment tools in ventilated newborn infants and evaluate their impact on pain management practices.
- To determine practices to assess and prevent withdrawal syndromes.

4.5 Secondary criteria

- Variations across European countries of the proportions of units that have developed and implemented local written guidelines for sedation and analgesia in ventilated neonates
- Identification and description of national guidelines for sedation and analgesia in neonates in all participating countries. Identification of recommended drugs.

5 STUDIED POPULATION IN EUROPAIN

5.2 Definition of the study population

- All neonates up to a corrected age of 44 weeks post conception. That means, for example, that a baby of 40 weeks gestational age can be included up to 28 days (4 weeks) of post natal age or that a baby of 32 weeks gestational age can be included up to 12 weeks of post natal age.
- The aim of including all neonates is to both ensure a generalization of the findings to all ventilated and non ventilated neonates admitted to intensive care units and to obtain a clear description of practices across Europe.

5.3 Recruitment centers

Neonatal units from all European countries will be invited to participate. Invitations to participate will be sent in each European country through official neonatal, pediatric or intensive care societies. Identification of these scientific societies will be carried out through international networks. In each country, a National Principal Investigator (NPI) will be designated by the EUROPAIN STUDY principal investigators in agreement with official national societies. The NPI is responsible for the coordination work within that country and for recruitment of units. If a unit from a country without a NPI wants to participate, this can be arranged with support from an existing NPI in another country.
Eligible are level III-units; i.e., units that will initiate and perform the full period of mechanical ventilation. Units that only perform intubations and then transfer neonates

to other units or ventilate neonates for short periods while awaiting transfer will not participate [40].
Each unit should have one responsible nurse, one responsible physician and one data quality manager. Figure 1 shows a diagram of the process to recruit centers.

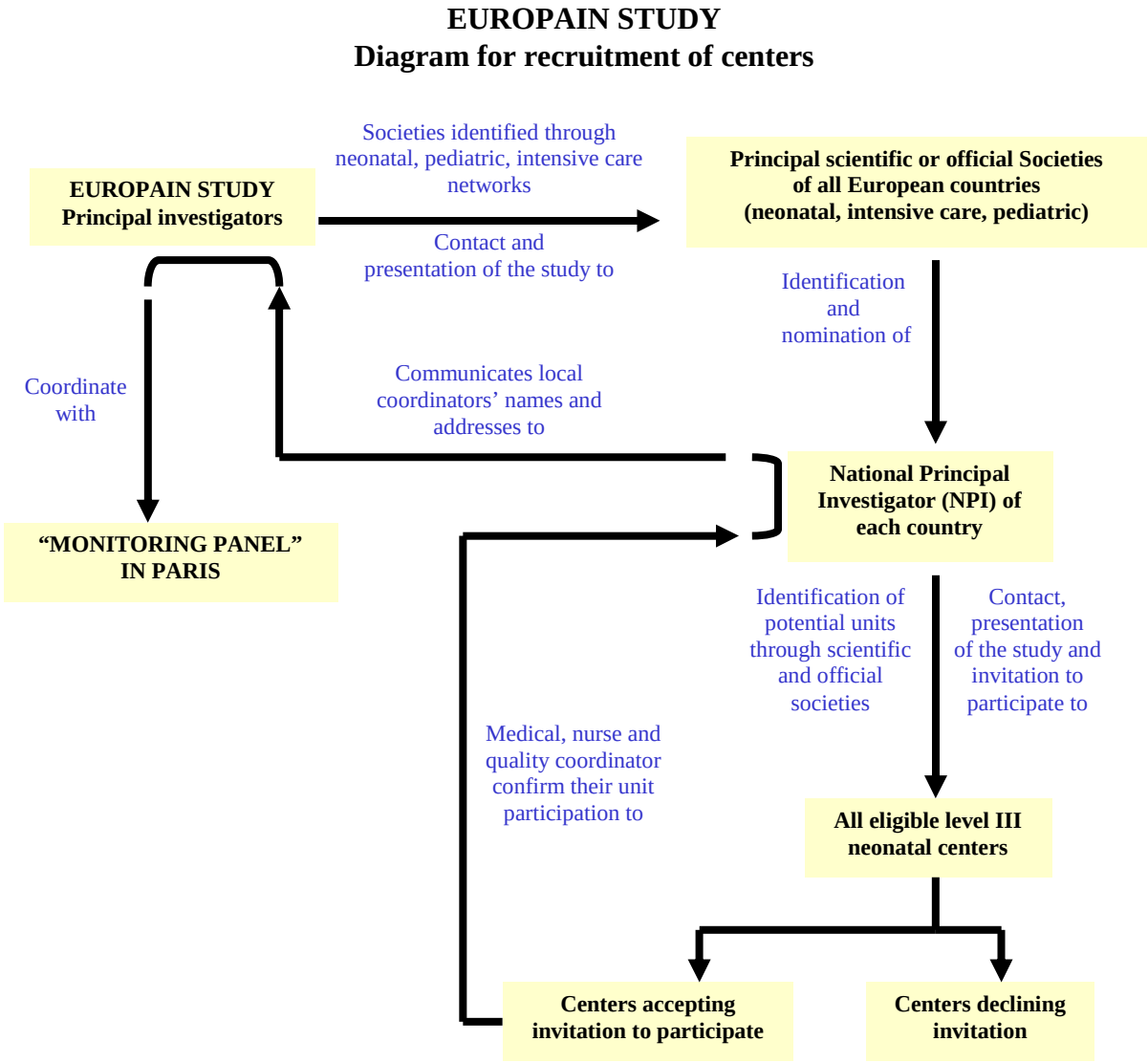


Figure 1. Flowchart of recruitment of centers

5.4 Inclusion criteria for neonates

The inclusion criteria are:

- All neonates up to a corrected age of 44 weeks post conceptional. That means, for example, that an infant born at 40 weeks gestational age can be included up to 28 days (4 weeks) of post natal age or that a baby of 32 weeks gestational age can be included up to 12 weeks of post natal age.

NOTE: Since this is an observational epidemiological study, all eligible infants of the unit during the study period should be included.

5.5 Exclusion criteria for neonates

- The only exclusion criteria of this observational study is the participation of the neonate in a research study including a randomization for the use of sedative or analgesic drugs in ventilated neonates.

6 INTERVENTIONS DURING THE STUDY

- AT THE PATIENT LEVEL
  The EUROPAIN STUDY is observational and therefore it will not interfere with routine practices of participating units. No changes in diagnostic, therapeutic or any managing strategy of patients are imposed by the participation in this study. This epidemiological study will only collect data on clinical practices in each unit.
- AT THE UNIT LEVEL
  No modifications of current managing protocols or strategies are requested by the participation in the EUROPAIN STUDY. The unit coordinators will only provide data on local protocols to manage procedural pain and sedation and analgesia in neonates as well as on general statistics of the unit.
- AT THE NATIONAL LEVEL
  The country coordinator will provide data on national guidelines to treat or prevent procedural or continuous pain in neonates.

7 PLANNING OF THE STUDY – EXPECTED PROGRESS OF THE STUDY

7.2 Type of study

- Epidemiological observational study.

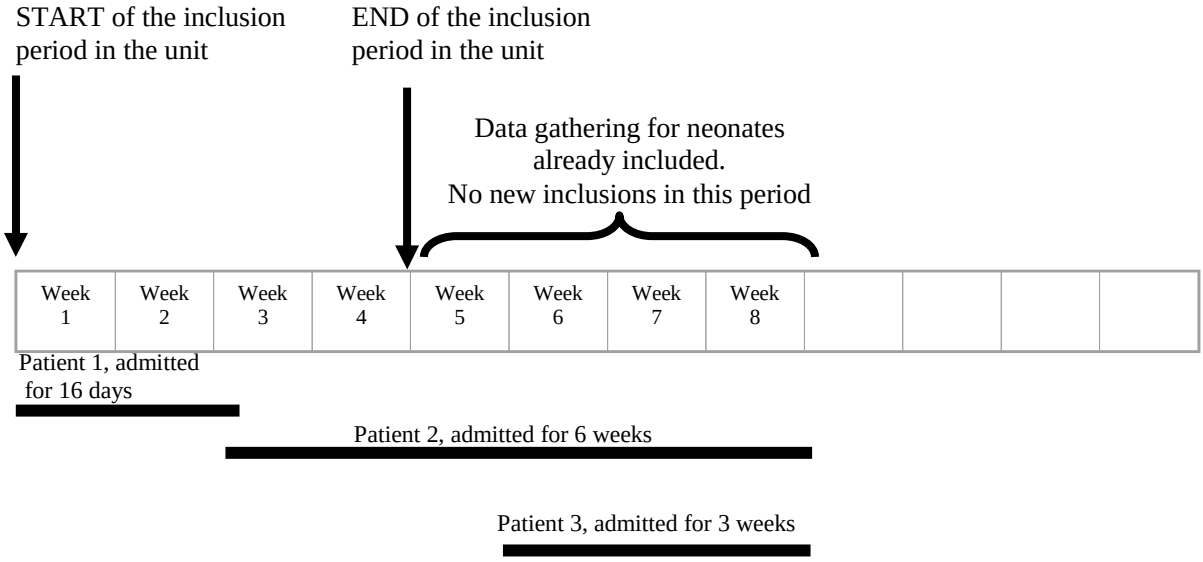
7.3 Organization of the study for the included neonates

7.3.A Definite inclusion of neonates

- This study will collect data on all neonates meeting the inclusion criteria as described above.
- The date of inclusion is the moment when the neonate fulfils the inclusion criteria.

7.3.B Data collection

- The duration of data collection for every included infant is 28 days. However, data collection will stop before 28 days if the infant leaves the unit (discharge, death, transfer to another hospital).
  Hereafter is shown a timeline illustrating an example of data collection periods for four infants (black bars). No infant is included after the eight week inclusion period but can, once included, generate data for a maximum of four weeks.



MAXIMUM DURATION OF DATA GATHERING FOR THESE EXEMPLES:

•Patient 1: 16 days

•Patient 2: the first 4 weeks (28 days) of admission

•Patient 3: not included in the study

- Data will be collected on individual data collection forms. These forms include demographic data, modes of respiration, continuous or intermittent sedative, analgesic or neuro-blocking drugs, pain assessment and drug withdrawal practices.
- Paper patient data collection forms are written in English with a subtitled translation in the country language. The web-based databases display questionnaires in the country language.
- The data collection forms will be completed by the unit nurse or physician coordinator or the person that they will designate.
- For each center, the duration of the inclusion period will be one month.
- Data will be entered on a secure web-based questionnaire.
- The inclusion period for different units will be decided by the NPI and the EUROPAIN STUDY principal investigators according to local facilities. Ideally, all centers should have their inclusion period during a phase of 6 months.

7.3.C Authorized treatments

- All treatments are authorized for included neonates since this study does not include any intervention.

7.3.D Follow-up after inclusion

- No follow-up after the end of the study period is foreseen for included patients

7.3.E Issues related to safety and protection of included neonates

- This observational study does not include any particular issue on the safety or protection of included infants since no intervention is planned on the participating infants. The routine safety and protection policies of each unit will apply when necessary.

7.4 Organization of the study for the participating centers

7.4.A Organization at the national level

- The National Principal Investigators will send invitations to join the study to all level 3 neonatal units of the country. The NPI will then communicate the names, emails and telephone numbers of the units that agree to participate to the EUROPAIN STUDY principal investigators
- The NPI is responsible for the coordination of all units in the country and ensures communication with the EUROPAIN STUDY principal investigators
- *Translation of data forms*. The original data-collection forms are web-based and have been written in English. However, these forms will be translated in the local language so that every center will fill in the forms in their own language. A printed copy of the questionnaire will be distributed to centers to be used as instructive material and/or as a preliminary support to gather data of included neonates. The questionnaires will show last name and first name

of the infant to serve exclusively as a mean to check inclusions and data entry at the unit level. Last name and first name variables will not be exported within the database that will be used for analysis. An automatic identification number will be generated for each new infant that is included in the study. Only this anonymous identification number will be exported within the database. The translation of all items into the local language will be performed with the help of the NPI. The National Principal Investigator will provide a translation of the forms, then, another native-speaker of the country will double-check this translation. In case of discrepancy, both translators will discuss the conflicting items. Since there are no subjective words or sentences in the forms, a validation of the content will not be necessary.

- The NPI will collect demographic data about the participating country, concerning socio-economics, health-care system, birth rates, perinatal mortality etc. Sources for these data are mainly official statistical documentation.
- In each country, the NPI will obtain (or designate someone to obtain) the national guidelines for neonatal pain management that may exist. Searches will be conducted through national health care boards, professional organizations and scientific publications. A standardized data collection form will be used to draw information from found guidelines.

7.4.B Organization at the unit level

- Figure 2 shows the main steps for the coordination between units and principal investigators
- A nurse and physician coordinator as well as a data quality manager will be designated for each unit.
- A web site will be created to post educational material for the study. It will include explanations for practical aspects of the study: how to fill-in data collection forms and how to enter data in specifically prepared data bases.
- The nurse and physician coordinator are responsible for informing all the unit staff about the study: rationale, inclusion criteria, period of recruitment, quality control, practical implications for the unit.
- A poster announcing the study will be distributed by email to all centers so that local staff be informed of practical aspects of the study.
- The medical coordinator or a person that he (she) will chose will enter the data from the patient's file into specifically designed web-based databases. The physician coordinator will report general statistics of the unit like number of beds, number of admission, year ventilator-days etc.
- Every unit will also report existing guidelines on sedation and analgesia in ventilated infants, including routines for withdrawal, procedural pain and on the use of pain assessment tools. Units will also be asked to send a copy of their guidelines to the NPI.

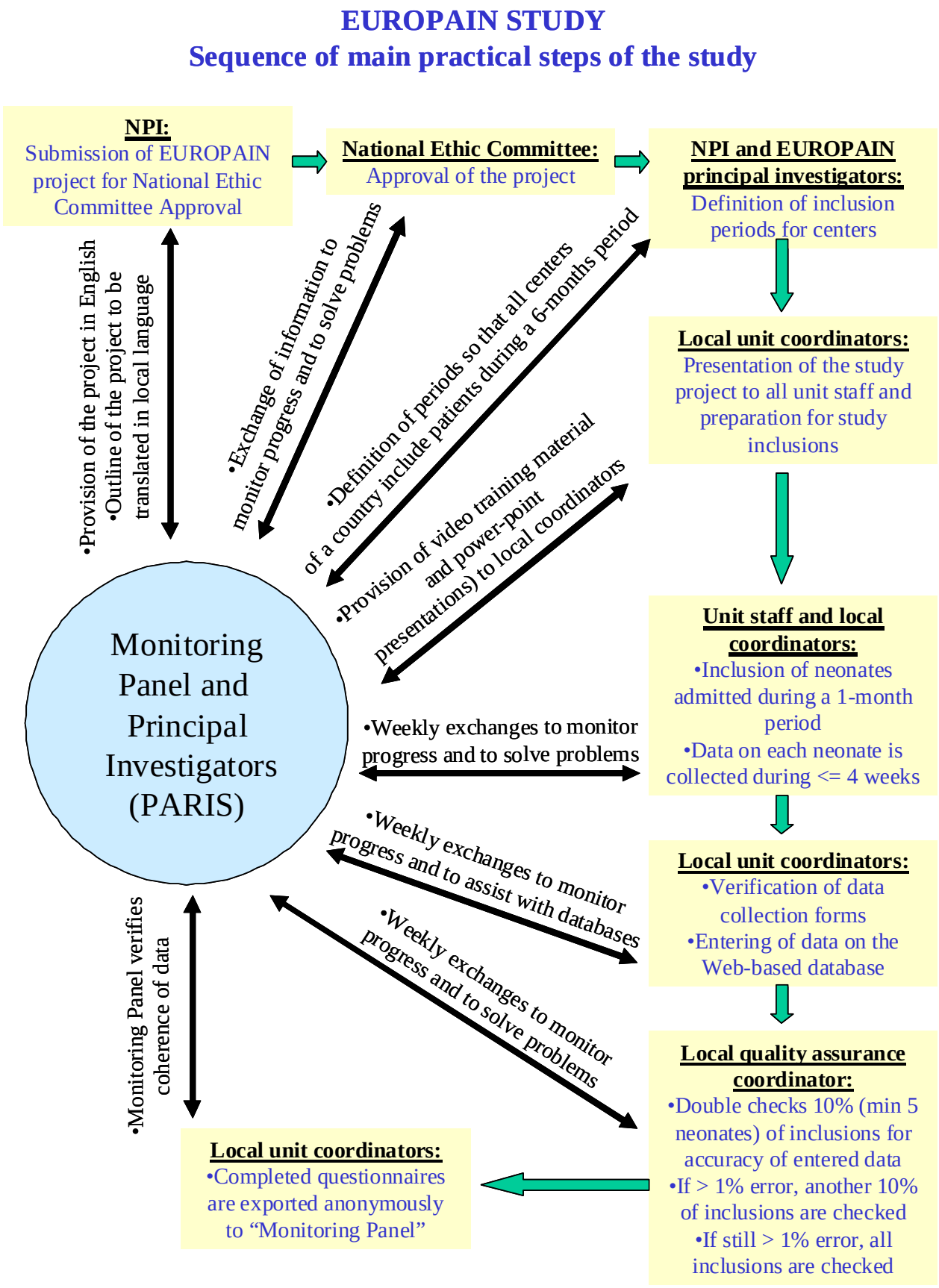


Figure 2. Diagram of the coordination process among units, NPI and principal investigators

7.4.C Preparation before study inclusions

- The staff unit should be informed of the unit participation in the study at least one month before the recruitment of patients.
- A power-point presentation with the outline and principal practical aspects of the study will be sent by the EUROPAIN STUDY principal investigators to local coordinators to serve as a support for local presentations of the study. This power-point presentation will be written in English, French and Spanish.

7.4.D Data collection and monitoring

- MONITORING PANEL. A monitoring panel will be created to monitor the progress of the study. This panel will ensure communication with all the participating units. This monitoring panel will be constituted by two persons working full-time during the study period. They will be stationed in Paris and working under the responsibility of EUROPAIN STUDY principal investigators.
- This panel will monitor the start of the study in each unit. They will contact, once a week, by email (or by telephone if necessary) the local medical coordinator to follow the rate of inclusions and to help with difficulties that may appear.

7.4.E Center Coordination

- The coordination at the center level will be conducted by the nurse and medical coordinator. They will be in contact with the National Principal Coordinator for the issues dealing with national coordination and with the "Monitoring Panel" for technical or conceptual issues.

7.4.F Country Coordination

- The National Principal Coordination will ensure that the maximum of eligible units of the country participate in the study
- The NPI will coordinate together with the EUROPAIN STUDY principal investigators the preparation of participating units and the study period for recruiting patients.

7.4.G All Center Coordination

- ***Educational material.*** The training of the participating staff will be carried out through Education material distributed by the EUROPAIN STUDY principal investigators. This material will provide information and training using short videos in three languages: English, French and Spanish. The nurse and physician coordinators will receive the links to educational material containing explanations of practical aspects of the study: how to complete data collection forms and how to enter data in specifically prepared data bases.

- The coordination of all centers regarding participating units, training, study material, data collection, entering data in databases, quality control will be conducted by the EUROPAIN STUDY principal investigators with the participation of the "MONITORING PANEL".
- The web site will be use to post all the useful material and inform participating units of the progress of the study.
- NPI as well as local coordinators will be contacted by email or telephone when necessary by EUROPAIN STUDY principal investigators or the "MONITORING PANEL".

8 STATISTICS

8.2 Justification of the duration of data collection and of number of included neonates

- It has been decided to collect data on each neonate for a period of 4 weeks (28 days). This decision is based on the fact that during the French Epippain study 97 out of 303 (32%) ventilated neonates stayed in the intensive care unit more than 2 weeks [32].
- We have planned to invite all the eligible units of each participating country with the aim of obtaining 20% of the nation units so that the results are representative of the country practices.
- ***Number of included neonates***. Regarding the number of neonates to include in order to show possible differences in the sedation and analgesia practices among the participating European countries, we have considered a scenario where differences are small. Thus, we have chosen an effect size (W) of 0.1. We have also assumed that 15 countries will participate. We have made calculations using the "Chi-Square Tests for Multiple Proportions" routine of the PASS 2008 software Power Analysis and Sample Sizes (NCSS, Kaysville, Utah). We have found that a total sample size of 2303 neonates will achieve 90% power to detect an effect size (W) of 0.1 using 14 degrees (15 centers) of freedom Chi-Square test with a significance level (alpha) of 0.05. Therefore, we aim at including an average of 154 neonates per participating country, less in smaller countries and more in big countries. Obviously, the number of neonates needed to include will be lower if the differences in sedation and analgesia practices among countries are larger.

8.3 Strategy for entering data in specified databases and data analysis

- Data will be entered in a web-based database created with the Voozanoo tool. This tool allows the creation of questionnaires to be used in the health related systems. This tool enables us to display menus and items in multiple

languages. The data will be entered locally in each center by the medical coordinator or the person that he will choose. The verified databases will then be exported to the “Monitoring Panel” The exported databases will contain neither last name nor first name of the patients. Records will be identified by an automatically generated number.
The database is at:
https://preprod.voozanoo.net/appli/VOOEUROPAIN/code/enquetes/663158034/

- **Data quality checking**. Quality control will be performed as a self-audit at the local hospitals. This quality control will be carried out by the quality control coordinator. It will be conducted on 10% of included neonates with a minimum of 5 neonates. The files to verify will be chosen randomly by the EUROPAIN STUDY principal investigators. The check should be performed by an independent person. We set up a limit of 1% errors in demographic and medical data. If this limit is exceeded, then another 10 % of charts should be checked. If still more than 1 % mistakes are found, all the charts should be double-checked. Found mistakes should of course be corrected and resubmitted.
  The data collection forms also have in-built protection against “impossible” values. At analysis we will also control for irrelevant clinical data.
- The "Monitoring Panel" under the supervision of EUROPAIN STUDY principal investigators will be responsible of Data management for all centers. The "Monitoring Panel" will run some verifications on the material received from centers to ensure that impossible or incoherent values are identified.
- The "Monitoring Panel" under the supervision of the EUROPAIN STUDY principal investigators will decide when to "freeze" databases.
- All databases will be copied and saved on a secure place.

8.4 Statistical tests to be used

- Chi-square test will be used to compare nominal data
- Comparison of continuous data following a normal distribution among centers will be carried out first with an ANOVA test and then pair wise comparisons will be done with Post Hoc tests.
- Comparison of continuous data that do not follow a normal distribution among centers will be carried out with the non parametric Kruskal-Wallis test. Then the pair wise comparisons will be done with a Mann-Whitney U test.
- Factors related with certain particular pattern of practices will be analyzed with multiple regression analysis models.

8.5 Place of data analysis and software to be used

- Data will be analyzed by a biostatistician at the EUROPAIN study center in Paris.

8.6 Main manager of data analysis

- The main managers of data analysis will be the Principal investigators: Ricardo Carbajal and Mats Erikson.

9 ETHICAL AND MEDICO-LEGAL ASPECTS

9.2 National principal investigators and centers

The list of NPI will be updates as new countries enter the study.

9.3 Investigators' engagements. Good research practices

- A pre-defined letter of engagement will be signed by all NPI and all center coordinators. This letter will include the respect of good research practices and will be sent to EUROPAIN STUDY national principal investigators before the start of the study.

9.4 National Statutory aspects

Since there is no uniform legislation concerning medical research across Europe, the general protocol will be adapted to comply with each country requirements.

9.4.A Promoter

- Since this is an observational study, it will not be necessary to have a promoter for this epidemiological study.

9.4.B Ethics committee

- The European survey of sedation and analgesia practices for neonates admitted to intensive care units will be an observational study. As such, it is a no-risk study since the investigators will observe and analyze information about practices but will not alter the care or services that neonates receive. Also, there is a very reduced potential for conflict between the investigators' role and the clinicians' role. Researches will comply, at all phases of the study, will national legislation of participating countries. The right to privacy and data protection will be of the utmost importance.
- In order to comply with recent guidelines issued for observational studies [41], the protocol will be sent to Ethics Committee Reviews of the participating centers, or at a regional or national level, depending on local legislation. The investigators will show the Committee how safeguards will be maintained to protect confidentiality and that the study has the goal of advancing health care practice. People conducting the survey will operate under professional standards or employment requirements that oblige them to maintain the confidentiality of patient data. It is possible that in some regions an expedited review will be done since it has been stated that expedited reviews are

appropriate for minimal-risk observational research that do not involve the collection of sensitive personal information. This survey will not involve processing of genetic information or personal data; it will only include de-identified data and anonymous demographic data.

- Investigators also commit to communicate results in a timely, understandable and responsible manner, so that benefit to the neonatal population is maximized and is fairly distributed.

9.4.C Informed parental consent

- Currently there is no need for a parental consent in observational epidemiological studies.
- Investigators conducting this survey will not obtain consent from parents to collect data on the practices of the participating units. Obtaining consent does not seem justified for the reasons exposed above and also because it is likely that explaining the background of this survey would create unnecessary anxiety for those whose consent will be sought and because the requirement for consent may create bias of recruitment and prejudice the scientific value of this study. In all cases, there will be no disadvantage or risk to the participants or their relatives.
- In countries where legislation requires that parents be informed that data on their infant is being recorded, an information letter will be given to parents. Parents will thus have the possibility of refusing the collection of data regarding their infant even if these data is anonymous.

9.4.D Center intention letter – Approval of patient recruitment

Once a center has agreed to participate, the local nurse and medical coordinator as well as the quality coordinator will send a signed letter of acceptance (U1) to the National Principal Investigator and the EUROPAIN STUDY principal investigators. The principal investigators in coordination with the NPI of the country will approve patient recruitment and announce the period of recruitment for that unit.

9.4.E Insurance

- Since the EUROPAIN STUDY is an observational study without any intervention in patient care, it will not need insurance to cover potential risks.

9.4.F Economical issues

- There is no possibility to financially reimburse participating units. Participation must be built on a will to contribute to the important research question, and the opportunity to belong to this research network.
- In the countries that participate to the NeoOpioid project and that have received a grant for this participation, the costs induced by the EUROPAIN STUDY will be covered by the received grant. For the other countries, local solutions must be sought to cover potential expenses. If printing or photocopying is a problem for a center, the French (AP-HP) or the Swedish

(Karolinska, Orebro) will search the best and fastest solution. The principal investigators from AP-HP will send printed material to centers if necessary.

- The training material and the preparation of databases will be financed by the grant received by APHP in France.
- No financial compensation will be given to centers for the inclusion of patients or entering data on the web-based database.

9.5 Modifications of protocol

- Any modification of the protocol has to be approved by the NEoOpioid Steering Committee constituted by the Principal Investigator from each partner in the consortium.

9.6 Anonymity of included patients

- The anonymity of patients will be respected and no patient name will be exported in the databases. Patients will be identified with a number indicating country, center and number in the center. A log list will be created at each center.

9.7 Duration of the study

We aim at limiting the inclusion period for each country to a period of six months. Each participating center will include all neonates fulfilling the inclusion criteria during a period of one month. Data on each neonate will be gathered for a maximum period of 4 weeks.

9.8 Storage of study documents

If paper data collection forms are printed in a center, these will be stored by the medical coordinator of each center. These forms will serve to enter the data into specifically designed web-based databases. However, data can be entered into the web-based questionnaire directly from the patient's file. The anonymity of patients will be respected at all exported databases. No exported database will contain the name of the infants. The principal investigators will save the databases in a secure place.

10REPORTS AND PUBLICATION ISSUES

Publication issues for Europain
We expect to prepare a main manuscript describing the general data and main results dealing with differences in practice in participating countries and one or two other manuscripts describing details in prescriptions of analgesics and sedatives as well as in pain assessing practices. The order of contributing authors in the papers will depend on their contribution to the study assessed by the number of included

patients and the proportion of participating units in the country. A total score will be obtained by giving an 85% weight to the number of patients and a 15% weight to the proportion of participating units compared to the total number of NICU units of the country. The attached excel file gives an example of the ranks.

For the first paper the expected order of contributing authors will be:
R Carbajal, 1st rank of national investigator, 2nd rank of national investigator, …last rank of national investigator, two members of the steering committee Neopioid consortium , E Courtois, M Erikson.

For the second paper the expected order of contributing authors
M Erikson, 1st rank of national investigator, 2nd rank of national investigator, …last rank of national investigator, two members of the steering committee Neopioid consortium, E Courtois, R Carbajal.

Members of the steering committee Neopioid consortium that are potential authors:
KJS Anand
H Langerkrantz
L Bergqvist

Once the main paper will be published, national data will be sent to national principal investigators so as they can publish their local data in national scientific journals.

11DATES AND SIGNATURES

EUROPAIN STUDY principal investigators

Ricardo Carbajal	Date: February 28, 2012	Signature .....
Mats Erikson	Date: February 28, 2012	Signature .....

Coordination of the study in Paris:

Emilie Courtois	Date: February 28, 2012	Signature .....

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