MASTER

The clinical value of continuous motion monitoring in neonatal intensive care units

Kaarem, R.E.

Award date:
2020

Eindhoven, 15-MAR-2020

The clinical value of continuous motion monitoring in neonatal intensive care units

by Rebecca Elena Kaarem

identity number 0926240

in partial fulfilment of the requirements for the degree of

Master of Science
in Human Technology Interaction
Eindhoven University of Technology

Supervisors:

prof. dr. J.H.D.M Westerink	Philips Research / Eindhoven University of Technology (IE&IS)
dr. D. Lakens	Eindhoven University of Technology (IE&IS)

Company supervisors:

ing. M. Meftah	Philips Research (Family care solutions)
dr. R. Joshi	Philips Research (Family care solutions)

Assessor:

dr. U. Matzat	Eindhoven University of Technology (IE&IS)

ACKNOWLEDGEMENTS

I would like to thank my thesis advisor Joyce Westerink from Eindhoven Technology of University for helping me throughout the final master thesis process. This included the search for a fitting project, guiding me throughout my research, writing of this thesis, and providing valuable feedback. Joyce consistently allowed this paper to be my own work, but steered me in the right direction whenever I needed it. She focused on my learning process and personal development.

I would also like to thank my supervisors Mohammed Meftah and Rohan Joshi from family care solutions at Philips Research. Rohan and Mohammed invested a lot of time and energy into ensuring high quality of my thesis by providing me with their expertise in the field of neonatal care. They also showed interest in improving my skills in doing research. Without our weekly discussions, writing a thesis in this complex field would be much more challenging.

I would like to acknowledge Daniel Lakens as the second advisor from Eindhoven University of Technology. Daniel advised me on choosing the right project, guided me throughout my research and writing of this thesis, and provided valuable feedback throughout the process.

I would also like to thank Willem Verkruijsse from Philips for introducing me to the project at Philips Research. I would also like to acknowledge my colleagues from family care solutions at Philips Research for always offering support and for creating a friendly work environment for me at Philips Research.

Finally, I must express my profound gratitude to my parents, my partner, and friends for providing me with support and continuous encouragement throughout my years of study and throughout my research and writing of this thesis.

ABSTRACT

Infants in neonatal intensive care units (NICUs) are vulnerable to health complications. Therefore, they are monitored mostly by their vital signs, e.g. heart rate and respiration. In addition, movement patterns and activity levels of infants are valuable in determining their pathophysiological state. These movements are only observed on an intermittent basis e.g. during nursing care, as nurses have limited time to spend on this extra activity due to other responsibilities. Furthermore, the observations are subjective, in which different nurses may interpret observations differently. Therefore, automated, continuous and objective motion-tracking technology might provide insightful information and assistance to nurses. In addition, early detection of the presence of and changes in specific movement patterns enables timely treatment and prevention of health complications. This research investigates the clinical value of movements of hospitalized infants by means of an extensive literature study, interviews and a survey. Relations of movement patterns with health complications and other clinical events were recognized in the literature, and semi-structured interviews were conducted to provide additional detail to these movement patterns in relation to the clinical events. A survey was conducted to test the validity of a number of relations/co-occurrences of movement patterns and clinical events. This resulted in a (partly) validated table linking specific diseases and clinical events to infant movement patterns, possibly enabling early detection of the diseases sepsis and NEC, clinical deteriorations of apneas, seizures, and (severe) cerebral hemorrhages, and the possibilities of monitoring pain/stress, sleep/wake and neurodevelopment in infants. Some associations between movement patterns and diseases/clinical events discovered in this research were firstly restlessness associated with infants who are uncomfortable or experiencing pain. Second, convulsions are typically associated with seizures in the literature, and this research discovered that these repetitive movements of convulsions are also associated with an infant with severe cerebral hemorrhage. Third, health care professionals (HCPs) recognized that infants who are experiencing pain show fast movements, as compared to a normal, comfortable state. Last, infants who are developing sepsis show movements with a small amplitude. Implementation of these movement patterns into motion-tracking technology have the potential to improve nursing care in NICUs.

Keywords: Unobtrusive monitoring, NICU, Infant motion

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	**Full description**
APIB	Assessment of preterm infant behavior
AS	Active sleep
CNS	Central nervous system
CP	Cerebral Palsy
DCD	Developmental coordination disorder
EEG	Electroencephalogram
EMG	Electromyogram
GMs	General movements
HCP	Health care professionals
HeRO	Heart rate characteristics monitoring
HR	Heart rate
HRV	Heart rate variability
IS	Indeterminate sleep
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
NAPI	Neurobehavioral assessment of the preterm infant
NBAS	Neonatal behavioral assessment scale
NEC	Necrotizing enterocolitis
NeoNEEDS	Neonatal necrotizing enterocolitis early detection score
NFCS	Neonatal facial coding system
NICU	Neonatal intensive care unit
NIDCAP	Newborn individualized developmental care and assessment program
NIPS	Neonatal infant pain scale
PIPP	Premature infant pain profile
QS	Quiet sleep
REM	Rapid eye movements
RR	Respiration rate
SpO2	Peripheral capillary oxygen saturation
TIMP	Test of infant motor performance
VLBW	Very low birthweight

1 INTRODUCTION

Most parents prepare for a complication-free, 40-week pregnancy period where they can return to their homes shortly after giving birth to a healthy infant. This scenario should not be taken for granted. In fact, more than 10% of neonates worldwide are born too soon, before 37 weeks of gestational age (WHO, 2019). This means an estimated number of 15 million preterm births yearly (WHO, 2019), which is a public health concern due to the many related complications of prematurity (The Lancet, 2016; WHO, 2019). Complications with prematurity introduce several challenges for the infants while making them highly susceptible to health deteriorations, such as various diseases, complications of future development, and mortality (Luca Cattani et al., 2017; Joshi et al., 2018). For instance, preterm births were responsible for around 1 million deaths in 2015 (WHO, 2019), primary causes being neonatal infections and respiratory failure (Cabon et al., 2017; Weber et al., 2003). Furthermore, complications related to prematurity is the leading cause of mortality among children under 5 years of age (WHO, 2019).

These complications originate from the late development of organs such as the brain and the lungs (Cabon et al., 2017; Joshi et al., 2018). Consequently, the early transition from the intra-uterine to the extra-uterine environment results in preterm infants being born while their organs are immature, and their autonomic nervous system is not fully developed (Joshi et al., 2018). An estimated three-quarter of these deaths could be prevented, possibly reflecting the increased attention towards the improvement of neonatal care in recent years (WHO, 2019). In fact, minimizing morbidity, future complications and mortality of preterm infants has become one of the targets of the UN sustainable development goals (SDG3.2), aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births by 2030 (WHO, 2019). One of the important factors for reaching this goal is the timely recognition of health complications. Timely recognition is important for facilitating correct treatment and nursing care, in order to minimize long-term sequelae (residual symptoms) and reduce the risks of complications (The Lancet, 2016; Watson, 2010).

Therefore, preterm infants' physiological immaturity and extreme vulnerability often result in their admittance to neonatal intensive care units (NICUs) (Joshi et al., 2018). The NICU is a specialized intensive care unit for preterm or critically ill infants, where neonatal is commonly applied to the first 28 days of life (Cone, 2010; Sardesai et al., 2011). Neonates in the NICU are routinely monitored mostly for vital signs, e.g. heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO2) (Joshi et al., 2018), as a representation of the autonomic nervous system (Als et al., 2005). Continuous monitoring of vital functions provides health care professionals (HCPs) with indicators of health complications e.g. monitor-alarms. These facilitate earlier detection of acute events e.g. absence of breathing, heart rhythm disturbances and a drop in blood oxygen saturation, and long-term complications e.g. disease onset (Chen et al., 2012). Monitoring of vital signs is informative and important to assist HCPs in their interpretation of the current health state of the infants (section 10.1 in Appendix A contains detailed information about NICU monitoring techniques).

In addition to monitoring of vital signs, however, HCPs highly rely on observing infants at the bedside. For instance, clinical observations such as skin color are useful to determine respiration issues (blue-grey color often relates to breathing problems). In addition, muscle tone and gross body movements entail valuable information about the health state of the infants, which is not easily captured by monitoring vital signs

(Joshi et al., 2018). Hence, observing and interpreting behavioral patterns enable nurses to deduce the wellbeing of the infant, as an addition to the information given by the monitors.

1.1 THEORETICAL BACKGROUND

A framework for the continuous interaction of behavioral subsystems of functioning within the infant and within the respective environments termed the synactive theory is depicted in Figure 1 (Als et al., 2005). This framework illustrates five independent subsystems within the infant. These subsystems are the autonomic nervous system, measures of the motor system (movements), state organizations e.g. sleep/wake behavior, attention/interaction, and the ability to self-regulate (Als et al., 2005). These five subsystems are in constant interaction with each other, the environment, and caregivers. These subsystems are referred to as cones in the original paper by Heidelise Als, and described as: "These cones are continuously in simultaneous contiguity if not interaction with one another, influencing and supporting one another or infringing on another's relative stability" (Als, 1982, p. 6). For example, a change in movement patterns (level 2 from the bottom) is expected before the outbreak of health deteriorations (Joshi et al., 2018). Furthermore, changing activity levels and movement patterns are indicators for sleep-wake patterns (level 3). Whether the infant attends and interacts (level 4) with specific stimuli such as the presence of the mother, bright light and noise, assist in determining whether there are problems with the physiological system (Joshi et al., 2018). Lastly, self-regulation (level 5), reflects infants' ability to maintain and/or regain a balanced, stable, and relaxed state (Als et al., 2005). Assessing the functioning of these various subsystems have assisted HCPs in determining wellbeing in infants (Als et al., 2005).

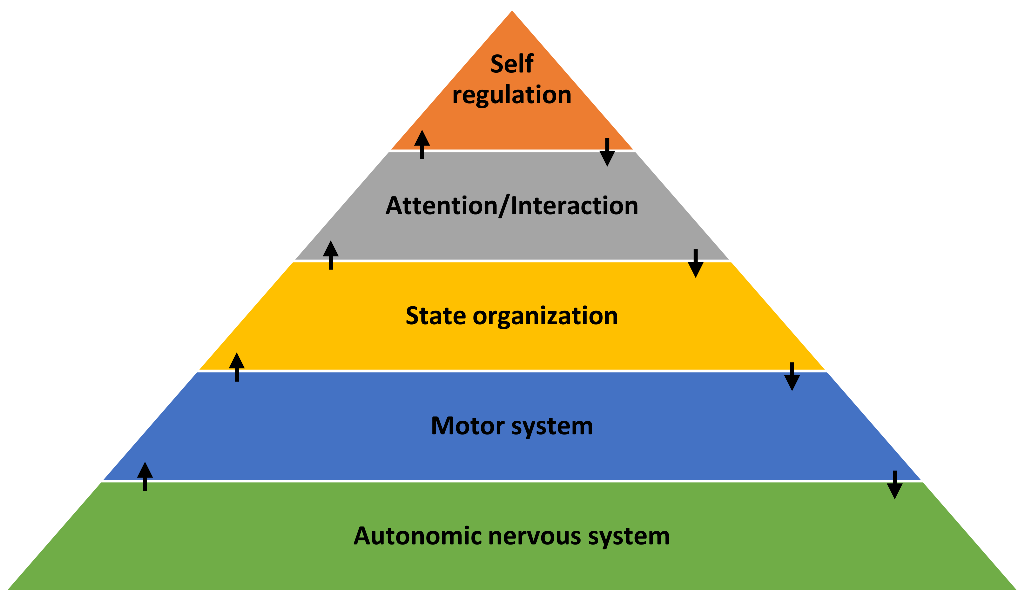

Figure 1: Illustration of the (modified) synactive theory (Als et al., 2005). The arrows illustrate that these five subsystems are in constant interaction with each other.

Motion in newborns (level 2) is recognized as one of the most crucial information sources to describe the pathophysiological state (Cabon et al., 2019). The well-known pioneer of early neurological development, Heinz Prechtl, recognized significant spontaneous motor behavior in early life as an important role for survival and adaptation (Hadders-Algra, 2004). The quality of these movements accurately reflects the condition of the nervous system in young infants (Hadders-Algra, 2004). For instance, sudden, involuntary movements are frequently displayed in newborns, either as a result of the immaturity of the central nervous system or of pathological, epileptic or non-epileptic origin (Facini et al., 2016). Detecting and understanding the differences of these movement patterns are important for proper diagnosis by clinicians (Facini et al., 2016), as it serves as early warning signs of clinical deteriorations e.g. infections (Joshi et al., 2018). Hence, observing changing movement patterns in infants may increase the likelihood of on-time treatment, reducing the risk of mortality and future complications in life for the infants (Joshi et al., 2018).

Currently, these movement patterns are assessed as part of the overall state evaluation of infants, e.g. with comfort assessment scoring tools such as “ComfortNeo”, shown in section 10.3 in

Appendix A. These observations are limited to the short caregiving periods and are to date fully reliant on subjective interpretations (Joshi et al., 2018; Verstraete et al., 2015). These subjective interpretations are prone to inter-observer variability, while being susceptible to observer fatigue, reduced attention, and limited to the sensitivity of our visual system (Hadders-Algra, 2004; Verstraete et al., 2015; Zuzarte et al., 2019). Consequently, this risks proper detection, quantification, and evaluation of movement complexity and variation in infants (Hadders-Algra, 2004), from a procedure that suffers from low inter- and intra-observer repeatability (Zuzarte et al., 2019).

Even though observation in the NICU is recognized as valuable, HCPs have limited time to spend on this extra activity due to other responsibilities. In fact, the complex, constantly changing NICU environment results in regular challenges for the HCPs, in addition to enabling an appropriate, safe environment for the high-risk patient group (Broom et al., 2018). For instance, noisy alarms requiring HCPs immediate attention often disrupt scheduled activities (Raths, 2009), as problems outside the routine checks regularly occur. This further risks occurrences of emotional distress and burnout for HCPs as discussed by Braithwaite (2008); Joshi et al. (2016) and Seys et al. (2013), which relates to alarm fatigue as discussed by Joshi et al. (2016). In addition, HCPs routinely interact with technologically complex equipment that is essential for infants' safety. Therefore, HCPs are required to understand and adapt to technological innovations. For example, the systems operating the current monitoring technology are composed of several wired sensors directly connected to the infant's body and the monitors outside the incubators (Luca Cattani et al., 2017; Chen et al., 2012). Hence, regardless of the severity level of deteriorations in the NICU, HCPs mostly rely on short observation periods and vital signs signals presented on the monitors for evaluation of infants' wellbeing, and for detection of health deteriorations, illustrating the infeasibility of constant bedside observation.

Therefore, movement-observations of infants in the NICUs are recognized as valuable to determine their health state, however, efficiency is restricted to short periods of observation, and the motion-data is not collected (Joshi et al., 2018). The monitoring possibilities of modern neonatal care have increased the chance of survival for prematurely born infants (WHO, 2019), in which additional/improved monitoring methods have the potential to add value to the observation of the health and wellbeing of neonates. Research highlight the promising value of long-term recordings of motion in infants (Cabon et al., 2019; Luca Cattani et al., 2017; Joshi et al., 2018; Zuzarte et al., 2019), such as detecting symptoms of deteriorations by detecting the presence or absence of rhythmic movements of one or multiple body parts (Luca Cattani et al., 2017). Based on annotators of video observation, Joshi et al. (2018) identified infants to be moving for 43.7% of the time, in which they further observed associations with periods of increased movement (bursts), increased HR and decreased RR and SpO2. Interestingly, motor responses often precede changes in vital signs, in which identifying changes in movement components potentially increase the ability for timely care and treatment (Joshi et al., 2018). The arguments above (among others) highlight the value of using technology to automatically and continuously monitor movements in infants (Cabon et al., 2019; Joshi et al., 2018).

Common limitations with the current monitoring techniques are that they are moderately invasive (especially for newborns), in which infants' fragility often limits the possibilities for additional long-term recordings of vulnerable infants’ physiological signals (Luca Cattani et al., 2017; Chen et al., 2012). Monitoring technology needs special care due to the infants’ fragile epidermis (top layer of the skin), in which electrodes attached to the skin should be avoided to prevent skin damage (Joshi et al., 2018; Sardesai et al., 2011). In fact, a single removal of an adhesive (e.g. for securing life-support devices) has shown capable of stripping off 70-90% of the epidermis (Sardesai et al., 2011), in addition to scarring, avoidance of skin damage is important to avoid sepsis and other infectious diseases (Zuzarte et al., 2019). Consequently, focus on continuous, non-obtrusive (contactless and non-invasive) monitoring methods for collecting data about underlying physiology in infants have increased, emphasizing the multidisciplinary involvement of integrated knowledge from medical science, design, technology and more (Cabon et al., 2019; Chen et al., 2012). Motion and movement monitoring is an option here, since it is contactless.

Research has dealt with and continues to deal with automated methods for monitoring. In spite of the technical challenges e.g. movement artefacts, clinical validation (Chen et al., 2012), and distinction of movements (Facini et al., 2016), several potential methods for long-term recordings of movements to monitor the physiological state of infants are proposed in literature. As traditional methods of monitoring motion with accelerometers are undesirable for this patient group (Zuzarte et al., 2019), automated processing of video and audio have received much attention for monitoring of preterm infants (Cabon et al., 2019). In addition, Joshi et al. (2018) proposed a motion-tracking technology based on remote sensors, in which a ballistic signal is extracted from a pressure film sensor embedded in the bedding of the neonate (ballistography[1]). The algorithm for tracking the motion has shown promising results in terms of accuracy, as it can function in real-time and possibly identify both acute and long-term clinical deteriorations (Joshi et al., 2018). Furthermore, a biosensor belt is reported for monitoring the heart rate, respiration rate, body movements and temperature of neonates with embedded sensors (Piccini, Ciani, Grövall, Marti, & Andreoni, 2008).

To date, however, a fully automated and efficient system does not exist, due to the challenges of integrating robust processing methods for long-term recordings in the NICU (Cabon et al., 2019). Nevertheless, there is need for a transition from adhesive to remote monitoring, and researchers are preoccupied with determining technologies for effective motion monitoring in the NICUs (Cabon et al., 2019; Joshi et al., 2018). This simultaneously calls for the correct understanding of infant movements (and underlying physiological interpretation) in relation to different clinical events. The underlying meaning of this relation should be communicated clearly by the technology running the algorithm, in order to facilitate proper reactions from the staff (see the illustration in Figure 2), fit the NICU workflow, and ensure reliability. Since the field of remote motion monitoring in the NICU is relatively new, a presentation of these aspects is not yet present in literature. Nevertheless, the synactive theory by Als et al. (2005) indicates that there is a relation between the motor system and clinical events/health deteriorations. The specific movement patterns, however, are not presented. Therefore, the research question is:

What is the physiological interpretation of various motion patterns exhibited by NICU infants?

The aim of this research is to identify the link between the motion signal and clinically meaningful information, as depicted in Figure 2. This goal includes the identification of useful clinical events for motion tracking technology, in order to recognize typical movement patterns for these clinical events (and relate these to technological feasibility), and to recognize the most important use-cases for these clinical events (with the related movement patterns). For instance, automatic notifications of critical deteriorations or pattern recognition algorithms estimating the optimal timing for nursing care. By

---

[1] Defined by Joshi et al., (2018) as: "Any approach for capturing forces generated by the body can be called ballistography, and includes forces due to body movement, breathing motion and the mechanical action of the beating heart".

focusing on improving nursing care, there is potential to improve the other quadruple aims as explained in section 10.2,

Appendix A.

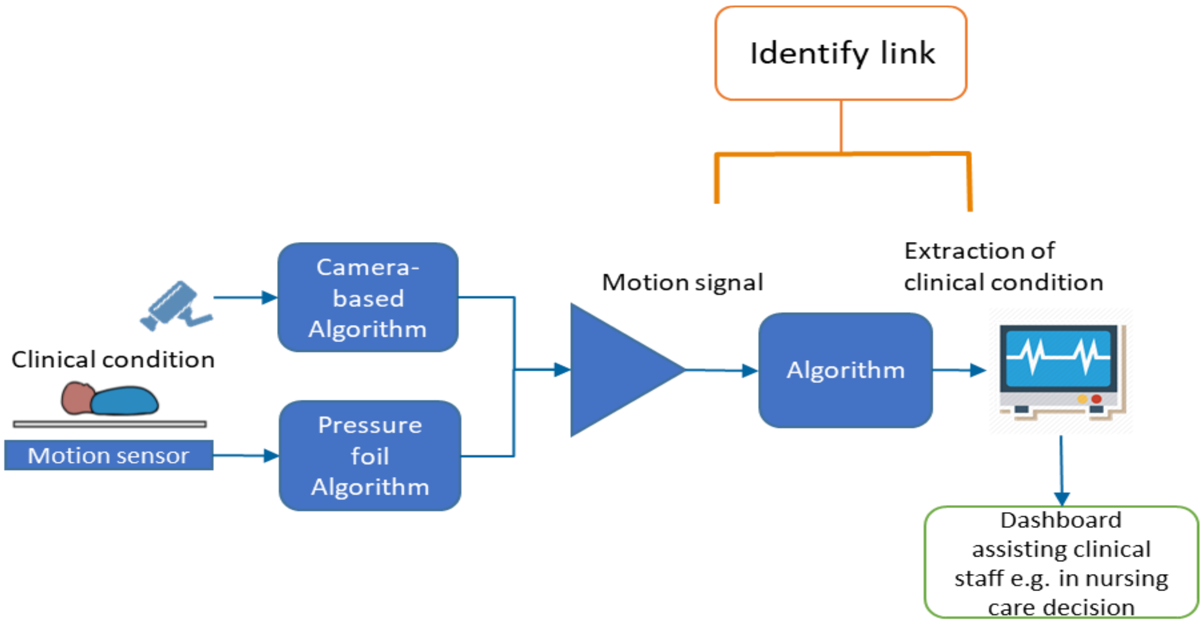

Figure 2: Illustration of the conversion of infant motion into clinically meaningful information. From the left, technology (a motion sensor and a camera) detects the movements of an infant, converts it into a motion signal, and feeds it into the algorithm. This algorithm extracts clinical meaningful information from the signal, and outputs the signal to the dashboard.

2 METHOD

As an answer to the research question, a so-called "encoding matrix" was developed, which links movement patterns in rows to relevant clinical events in columns. Thus, the matrix highlights when a specific movement type is reflective of important information about a specific clinical event. The encoding matrix was developed in a 3-step process as depicted in Figure 3, involving literature study, expert interviews, and a survey. Section 2.1 and 3 describe the method and results of the literature review respectively. Section 4 describes the method for the interviews and the survey, whereas sections 5 and 6 present the results of the interviews and the survey respectively.

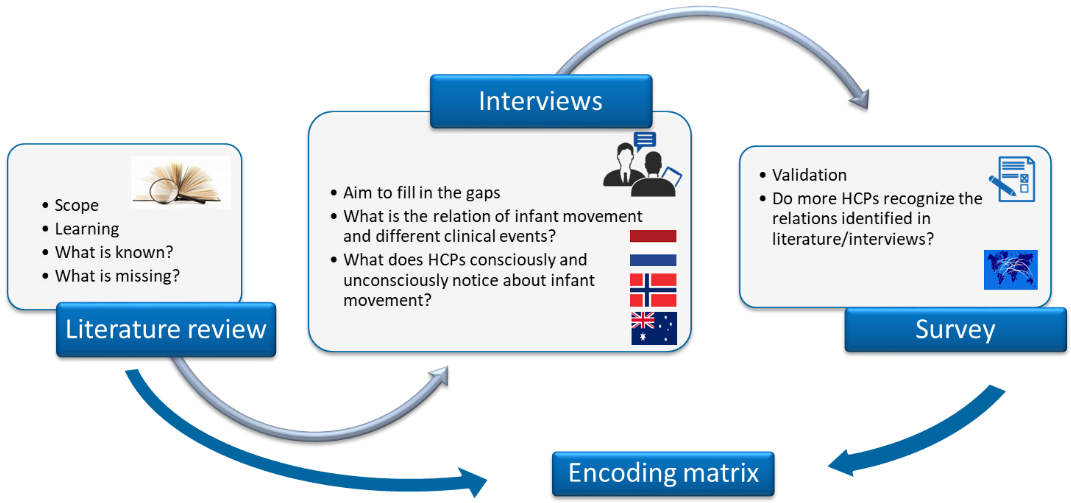

Figure 3: Illustration of how the methodology aims to answer the research question

2.1 METHOD – LITERATURE REVIEW

The large content area of neonatal health and deteriorations required an explorative review approach, where a semi-systematic review approach was used. This is a suitable approach for reviewing literature within topics that have been studied by various groups of researchers (Snyder, 2019).

As a first step, a selection of relevant articles provided by Philips Research within the field of neonatal monitoring was read. After thoroughly reading and analyzing these articles, specifically Joshi et al. (2018) and Cabon et al. (2019), relevant articles from the reference list of these papers were selected. This iterative process continued for a few cycles, before new search queries were created for the specific topics that started arising as the literature review unfolded. For instance, search queries for the clinical event "sepsis" included "sepsis AND (movement OR activity OR motion)". After gathering information for each clinical event, more specific motion pattern queries were used such as "sepsis AND lethargy" or "pain AND grimace", which eventually resulted in separate, more detailed queries during the process of broadening the knowledge span while simultaneously collecting large amounts of qualitative data.

Within this semi-systematic, explorative approach, a list of relevant clinical events for movement-tracking technology was created. This was done by firstly noting down each clinical event that was mentioned in three or more of the read papers. As the final list was extensive, the selection of the clinical events chosen to focus on in this study was based on prevalence (frequently reported diseases in the NICUs), the severity of the condition, and repetitiveness in literature. This list assisted in the recognition of clinical events with potential value while discovering the current knowledge of (pre)term infant motion in general. Secondly, the literature review assisted in exploring whether scientific papers within the field had discovered movement patterns for the different clinical events, and what these movement patterns are. Similar to the list of clinical events, all of the recognized movement patterns for each clinical event were included in a list of movement patterns. After collecting all the movement patterns, each movement pattern on the list was inspected and compared with the other movement patterns on the list, to check for similarities. In addition, several rows of movement patterns that described subtle movement patterns, were fused into more general movement-pattern categories when applicable. For instance, brow bulge and eye squeeze were fused into the movement-pattern category grimace.

The literature review resulted in a (preliminary) list of clinical events, which would be further developed in the interviews with experts in the field, and serve as columns to the encoding matrix. In addition, it resulted in a (preliminary) list of motion patterns, which would later be tweaked in the interviews with experts in the field, and will serve as the rows of the encoding matrix. Each paper that mentioned each movement pattern in relation to a clinical event was tracked by means of a list with names for each reference (L1, L2, etc.) that were included in the cells of the preliminary version of the encoding matrix.

3 RESULTS – LITERATURE REVIEW

Following the procedure described in section 2, the upcoming subsections present the elaborate results from the literature review that lead to the first version of the encoding matrix. A number of clinical events are identified, that depict the columns of the encoding matrix. For each of these clinical events, movement patterns are identified, which depicts the rows of the encoding matrix. The encoding matrix shown in Table 1 serves as a summary of the upcoming sub-sections, that will describe how the cells of the encoding matrix are filled in. This matrix is grouped into posture, activity level, and movement patterns, where the movement patterns are further grouped into body areas where the movements occur. The cells that are considered to have strong evidence from the literature (mentioned by at least 2 articles) are highlighted in blue.

Table 1: Encoding matrix based on the literature review. The red numbers indicate the scientific article code the information resembles. Blue numbers are scientific articles that indicate the relation, but the relation is not clearly defined. The list of the articles related to each article code can be found in Table 8 in section 12.1 in Appendix C. The cells that are highlighted in blue are the cells that contain more than one scientific article highlighting the relation in the literature and are therefore considered to have enough evidence. The labels containing a star are described below the table. Detailed explanations of all the rows are found in section 12.2, Appendix C.

Cells that contain more than one scientific article that indicate the relation

Clinical event / Posture	Discomfort / stress	Pain	Sepsis	NEC	Cerebral Hemorrhage	Seizure	Apnea
(Repeatedly move) out of fetal position	L33, L34	L33, L34					
Overall activity level (gross body movement)/Clinical event							
Increase / active		L5	L14				
Lethargy			L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16	L17			
Movement patterns/Clinical event	**Discomfort / stress**	**Pain**	**Sepsis**	**NEC**	**Cerebral Hemorrhage**	**Seizure**	**Apnea**
Abnormal movement pattern (different movements from normal)							L21, L24, L31 (struggling/ thrashing)
Cramps/tremor/ tremulousness	L3, L36	L36					
Convulsions*			L7, L8, L10, L11, L13, L14, L15, L20 (term)		L9	L2, L8, L9, L21, L22, L30	
Startles (shock, repeating)	L3, L36	L37, L35, L36 (decrease)					
Twitches	L36 (extremities)	L37, L35, L36 (decrease) (extremities)			L9	L9	
Head/Neck							
Moving head downward						L19	
Grimace*	L4, L37	L5, L26, L33, L34, L35, L36, L37					
Repetitive face movements*	L1, L2	L34, L37, ComfortNeo				L9, L21, L22, L30	

Tongue extension	L37	L36, L37					
Specific eye movements*	L1, 37	L37				L2, L21	
Torso/trunk							
Diffuse squirm /wriggling the torso	L36	L36					
Absence thoracic movement (up/down) (absence of periodic breathing movement)							L9, L21, L24, L31
Arching of the back	L36	L36					
Limbs							
Absence of periodic breathing movement							L9, L21, L22, L24
Jerky movements						L2, L20, L19	
Extension of limbs	L36, L37	L5, L36	L13*		L9, L20, L21 (decerebrate posturing)	L9, L19, L20, L21, L28, L29 (like decerebrate)	
Repetitive extension/flexion movement	L37	L5, L33				L2, L8, L9, L21, L22	
Flexor movements	L37	L5 (arms), L36					
Speed of movement							
Slow						L20, L22	
Fast						L20, L23	
Low frequency of movements (<6 Hz)						L29, L19, L27, L32	
Amplitude of movement							
Small range (<3 cm)							
Large range (>3cm)						L29, L19, L27, L32	
Hand/foot clasp	L36	L36					
Upper limbs							
Salute* – extension of arms into midair in front of infant	L4, L36, L37	L5, L36, L37					
Airplane – extends arms laterally	L36, L37	L36, L37					
Grasping /Pulling/grabbing	L36, L37	L36, L37					
Hands							
Hand on face / Hand to mouth	L36, L37	L36, L37					
Fisting	L4, L36	L5, L36					
Finger splay	L36, L37	L5, L35, L36					
Lower limbs							
Extension of lower limbs (specifically)		L5, L37			L9, L20, L21 (Decorticate posturing)	L9, L19, L20, L21, L28, L29 (Decorticate posturing)	
Repetitive flexion-extension movements of lower extremities	L37						
Sitting on air: full extension of legs into the air	L36, L37	L36, L37					

*Convulsions: Repetitive, stereotyped non-suppressible motor movements, rapid and repeated contractions/relaxations of the muscles, sustained, rhythmical jerking or sudden, periodic and involuntary (violent and irregular) movements of limbs, with flexion/extension phases that are different in amplitude, ocular phenomena, and movements involving the jaw and the extremities. *Grimace: includes brow bulge, eye squeeze, nasolabial furrow, wide-open mouth/yawning, *Repetitive face movements: include face twitch, excessive sucking, yawning, *Specific eye movements: contains eyes unfocused and uncoordinated/floating, *Extension of limbs for sepsis: translated from “stiff limbs”, *Salute: contains vertical movement in space, and flexed high guard arm position with fisted hand.

The first result of the literature review was the selection of the rows and columns of the encoding matrix. Manifestations of diseases and other clinical events are commonly seen in the vulnerable patient population in the NICU. Therefore, the focus of clinical events in this report narrows down to the diseases sepsis and necrotizing enterocolitis (NEC). Furthermore, the other clinical events are often indicative of potential diseases, in which focus will be on apneas, cerebral hemorrhages, seizures, general comfort/discomfort, neurodevelopmental aspects and sleep/wake behavior of infants. These clinical events were selected based on the impacts on infants' life and the severity level, and the first seven clinical events are described individually in the upcoming sub-sections. The last two clinical events (neurodevelopment and sleep-wake behavior) had more specific movement patterns as compared to the more common patterns recognized in the other clinical events. Therefore, these results are presented with the same structure in sections 11.1 and 11.2 in Appendix B. Each subsection firstly describes the importance of the selected clinical events for the columns, followed by the related movement patterns. These movement patterns are marked in blue throughout the subsections. For the interested reader, the vital signs associated with each clinical event can be found in section 12.3 in Appendix C.

3.1 SEPSIS

3.1.1 Disease description and impact

Sepsis is a whole-body inflammatory response to an infection e.g. pneumonia, triggered by an immunological response (Chiesa, 2004; Shane & Stoll, 2014) injuring its own tissues and organs (Ambati et al., 2016; Kudawla et al., 2007; Weber et al., 2003). Sepsis is a major cause of morbidity and one of the primary causes associated with neonatal mortality worldwide (Ambati et al., 2016; Cabon et al., 2017; Weber et al., 2003). In fact, sepsis and other infectious diseases account for 26% of the estimated 4 million annual neonatal deaths (Rosenberg et al., 2010), and preterm infants are at high risk of developing this life-threatening condition (Joshi, Kommers, et al., 2019). Neonatal sepsis requires timely identification and treatment (Kudawla et al., 2007; Weber et al., 2003), as delayed antibiotic treatment is associated with high mortality and adverse long-term consequences (Fairchild, 2013; Joshi, Kommers, et al., 2019). The gold standard for diagnosis is a blood culture, which is a time-consuming procedure (typically 24 hours or longer to obtain) (Joshi, Kommers, et al., 2019; Rosenberg et al., 2010; Verstraete et al., 2015). In addition, blood cultures are prone to false positives as a result of contamination during collection (due to skin commensals), or false negatives because of the low blood culture, being a major issue with premature infants (Chiesa, 2004). Furthermore, once obtaining a positive result, the identification of causing infection/bacterial strain requires additional time (Joshi, Kommers, et al., 2019). The severe consequences of sepsis in infants have resulted in a rather low threshold for initiation of antimicrobial therapy (Bekhof et al., 2013). This is non-ideal, due to the risks of antimicrobial resistance development or other adverse outcomes of inadequate or unnecessary treatment (Verstraete et al., 2015). Because the current gold standard for identification of sepsis is an invasive, time-consuming procedure, there is an increased focus on developing prediction models based on other clinical signs (Verstraete et al., 2015).

3.1.2 Movement patterns associated with sepsis

Weber et al. (2003) did a multivariable analysis of 14 independent predictors and found that the presence of at least one of 14 tested signs was an independent predictor of severe disease (including sepsis, meningitis, hypoxemia[2] or radiologically proven pneumonia). These 14 signs included no spontaneous movement, temperature > 38°C, being drowsy/unconscious, a history of change in activity, agitation,

[2] Hypoxemia is a cardiac event where the oxygen level in the blood is abnormally low (SpO2 <80%). (Weber et al., 2003).

respiratory rate > 60 breaths/min, and history of convulsions[3]. Their results had a sensitivity of 87% and specificity of 54%. Rosenberg et al. (2010) found similar results in an attempt to validate the score developed by Singh et al. (2003), with a low sensitivity (56.6%) but a high predictive value (78.1%). By creating their own five-sign model, they received a predictive value of 64.9% (sensitivity 77.1%) for at least one clinical sign (including apnea[4] and lethargy).

Lethargy, meaning decreased spontaneous infant activity, reduced overall movement (Joshi, Kommers, et al., 2019), and that infants move more slowly than normal (Rosenberg et al., 2010), is the current best predictive clinical sign of sepsis (Rosenberg et al., 2010; Singh et al., 2003; Zupanc, 2004). This has been validated in several studies; Verstraete et al. (2015) found lethargy as the most frequent sign in a meta-analysis of 9 studies containing 5 clinical prediction models, and Kudawla et al. (2007) reported lethargy as a predictive clinical sign in 46% of the occurrences. Ambati et al. (2016) found in an observational study of 419 infants in the NICU at Mahatma Gandhi Memorial Hospital that lethargy (63%), respiratory distress (44%) and depressed neonatal reflexes (45%) were among the most common manifestations of proven (blood culture) sepsis. In addition to lethargy, hypothermia[5] and apnea/bradycardia[6] are more commonly present in preterm infants (Verstraete et al., 2015), while convulsions and hyperthermia[7] are more common in term infants (Ambati et al., 2016). Furthermore, Joshi et al. (2019) found a reduction of spontaneous movements (lethargy) in the period (hours) leading to the CRASH-moment (Cultures, Resuscitation, and Antibiotics Started Here), in which lethargy/decreased movement corresponded to an increased probability of sepsis. Van den Bruel et al. (2010) have also suggested the presence of stiff limbs in a lethargic, septic infant.

Furthermore, convulsions are recognized as predictors of serious infection (Rosenberg et al., 2010; Van den Bruel et al., 2010; Verstraete et al., 2015; Weber et al., 2003). Sankar et al. (2008) suggested that convulsions occurring on day 4-7 of life have a higher chance to relate to sepsis, meningitis and metabolic causes. Singh et al. (2003) however mentioned that convulsions may occur too late or infrequently for predictor/early diagnosis.

Although research highlights several predictive signs of sepsis, combinations of several predictive signs might be necessary for accurate prediction, especially in premature infants (Verstraete et al., 2015), as lower birth weight increases the chance of non-septic conditions clinically mimicking late-onset neonatal sepsis (Singh et al., 2003). In addition, detecting a change in the presentation of that predictive sign rather than the presence of one predictive sign e.g. measuring "increase of" and "acute onset of" strengthens clinical relevance (Verstraete et al., 2015; Zupanc, 2004). The combinations and changes in these predictive signs should be combined with vital signs, setting, birth weight, and gestational age, for accurate prediction (Griffin et al., 2007; Verstraete et al., 2015). One important consideration is to combine the movements related to sepsis with the movements related to apneas. This is because an increased tendency of apneas (compared to a patients' baseline), in particular, mixed apneas (Poblano et

---

[3] Convulsions are specific movement patterns associated with pathological seizures, and are described in detail in section 3.5.1

[4] Clinically defined as an episode with the absence of breathing, lasting at least 20 seconds, or less (10 – 20 seconds) if associated with other clinical signs/symptoms (L. Cattani et al., 2014; Lee et al., 2012).

[5] Abnormally low body temperature

[6] Slowing of heart rate, usually classified as lower than 80/100 beats per minute (Finer et al., 2006; Lee et al., 2012).

[7] Abnormally high body temperature (fever)

al., 2006) is seen during sepsis build-up, being an important sign of early suspicion of sepsis (Ambati et al., 2016; Fairchild, 2013; Rosenberg et al., 2010; Verstraete et al., 2015).

3.2 Necrotizing enterocolitis (NEC)

3.2.1 Disease description and impact

NEC is a disease of gastrointestinal illness (Fox et al., 2015; Gephart & Quinn, 2019) caused by an inflammatory process in the intestines (Neu & Walker, 2011). This inflammation is often caused by damage to the tissue on the inner lining of the intestines (Healthline, n.d.). For severe cases of NEC, hole formation on the intestine wall may be developed, where bacteria from the intestine may spread to the abdomen and cause infection (Healthline, n.d.). NEC is among the most common and devastating diseases in neonates (Neu & Walker, 2011) with mortality rates of 20-30% (Fitzgibbons et al., 2009), recognized in 2-12% of very low birth weight (VLBW) infants, <1500 gram (Gephart & Quinn, 2019). Lifelong impacts such as poorer neurological outcomes are found for surviving infants (Gephart & Quinn, 2019; Neu & Walker, 2011). Early diagnosis of NEC is challenging, as there is a lack of clinical diagnostic tools (Fox et al., 2015). Therefore, recognition of NEC is normally delayed until clinical signs such as feeding intolerance and intestinal dilation/distention are present (Grave et al., 2007; Stone et al., 2013). Findings from Gephart & Quinn (2019) suggested that the majority of NICUs do not have a standardized process to quantify the risk of NEC or to recognize and communicate early NEC warning signs. Tools such as the heart rate characteristics (HeRO) monitoring system, pediatric early warning score, and feeding tolerance algorithms were used in some NICUs. Literature has highlighted the need for early detection methods for NEC, and more consistent clinical decision support systems to improve NEC detection/prevention practices (Gephart & Quinn, 2019).

3.2.2 Movement patterns associated with NEC

Stone et al. (2013) found and Fox et al. (2015) further validated a range of clinical cardiorespiratory systemic signs and symptoms (including apneas) preceding NEC occurrence and worsening during the disease. This initiated the development of the clinical symptom scoring tool Neonatal Necrotizing Enterocolitis Early Detection Score (NeoNEEDS). This tool accounts for risk factors such as low gestational age (<28 weeks) and low birth weight (<1000g), in combination with other predictors to create a "risk of NEC" score (Fox et al., 2015). Similar to assessment of sepsis, a behavioral score of 0 (no obvious risk) was given to alert/active infants, 1 to infants showing drowsiness and decreased activity, but still responded to stimulation, and 2 (highest risk) to lethargic infants with minimal response (including other parameters e.g. abdominal changes and feeding tolerance) (Fox et al., 2015). Fox et al. (2015) found that NeoNEEDS significantly decreased NEC severity by assisting nurses and other caretakers in recognizing baseline changes in infants, which in turn triggers evaluative processes, that allows for earlier intervention to abnormal findings. In addition, practices within NICU was found to heavily contribute to varying NEC rates between NICUs, in which better feeding protocols, minimizing exposure to antibiotics, and specifying an approach for timely recognition have reduced severity (Gephart & Quinn, 2019). This illustrates that there is potential for improved NEC detection methods.

3.3 Apnea

3.3.1 Clinical event description and impact

Apnea is the cessation of breathing for a short time, commonly occurring in premature infants (Lee et al., 2012; Newnam & Parrott, 2013). Apneas occur in more than 50% of premature infants and almost always in infants less than 1000 g at birth (Finer et al., 2006; Lee et al., 2012). The majority of infants are apneic due to prematurity, sepsis or respiratory problems (Joshi et al., 2018), but also as an effect of other clinical problems such as hypoxemia, neurological injury, or a symptom of seizure manifestation (but rarely the only symptom) (L. Cattani et al., 2014; Joshi et al., 2018; Lee et al., 2012). In addition, symptoms of apneas normally increase during and after feeding, possibly due to the immature coordination between breathing, sucking and swallowing (Poets, 2010). Serious clinical events of apnea are often accompanied by bradycardia or oxygenation desaturation, so-called ABD events, which requires immediate attention for assessed pathology (Finer et al., 2006; Lee et al., 2012; Poets, 2010; Rosenberg et al., 2010; Williamson et al., 2013). Assessing pathology is important as apneas may be a first symptom of a more significant medical issue (e.g. sepsis) (Newnam & Parrott, 2013). In addition, timely detection (immediately upon cessation of breathing) of apnea is important in order to initialize treatment (e.g. increasing ventilatory support), as episodes of apnea can be deadly (L. Cattani et al., 2014).

Apneas are typically classified into three types based on the presence or absence of obstruction of the upper airway. *Obstructive apnea* is a blockage of the airway (Lee et al., 2012). *Central apnea* is a cessation of the respiratory drive (inspiratory effort), without upper airway obstruction, in which the infant makes no effort to breathe (L. Cattani et al., 2014; Facini et al., 2016; Lee et al., 2012). Central apneas indicate immaturity of respiratory control (Lee et al., 2012). *Mixed apneas* typically begin with an obstructive event, and then change to central apnea (Lee et al., 2012), hence, a mix of an obstructed airway and periods of central pauses (Newnam & Parrott, 2013).

The most common modality for monitoring respiration and detection of apneas rely on chest impedance monitoring, measuring changes in impedance as the lungs fill with air (which is a high impedance substance), detected through the ECG electrodes (Lee et al., 2012). There are several drawbacks with the long-term use of this method such as discomfort and skin irritation (and potential scarring) especially in preterm infants (Joshi, Bierling, et al., 2019). In addition, the cardiac signal (blood pumping through the heart) during apnea might be mistaken for breathing (Lee et al., 2012), possibly also a reason for many apneas being under-detected by monitors (Joshi et al., 2016)..

3.3.2 Movement patterns associated with apneas

Features from infant (spontaneous) movement patterns have been recognized either as predictive for causal reasons (e.g. movements triggering hyperventilation) or symptomatic reasons (movements occurring as a response to an underlying physiological change) (Joshi et al., 2018; Williamson et al., 2013). As breathing is characterized by periodic movements of specific body parts, the most recognized sign of central apnea is the absence of periodic breathing movements on the limbs and/or the chest (L. Cattani et al., 2014; Facini et al., 2016; Lee et al., 2012; Zupanc, 2004). Obstructive apneas are often accompanied by struggling or "thrashing" movements of the infant as explained by Lee et al. (2012), as the infant's chest wall moves without sufficient airflow through an obstructed airway (L. Cattani et al., 2014; Facini et al., 2016; Lee et al., 2012).

Motion monitoring could be an important marker for predicting apnea (Joshi et al., 2018), in which movements alone or in combination with vital signs by for example removing impedance changes of the heartbeat ease the process of detecting the absence of chest movements during apnea (Lee et al., 2012). Accurate detection methods have shown potential in improving apnea detection in the past, in which Lee et al. (2012) detected a higher number of apneas with an automated detection system, compared to the nurses' records of the current system. Joshi et al. (2019) found promising results of monitoring respiration with a pressure sensor placed underneath the bedding of infants in the NICU. Furthermore, a video camera could e.g. acquire chest movements (L. Cattani et al., 2014), and estimate their periodicity (Luca Cattani et al., 2017)

3.4 Cerebral hemorrhages

3.4.1 Clinical event description and impact

A cerebral hemorrhage, in particular intraventricular hemorrhage (IVH), is a bleeding into the ventricular system of the brain caused by fluctuations in cerebral blood flow (Elser et al., 2011). IVHs are classified on severity grades 1-4, in which grade 3 (blood distending the lateral ventricles - pressing on brain tissue) and 4 (blood within ventricle system and parenchyma[8] – directly involves brain tissue) (Poryo et al., 2018) are predictive of other complications such as blindness, mental retardation and cerebral palsy[9] (Whitelaw & Lee-Kelland, 2017). A cerebral hemorrhage is a serious complication in preterm infants, with occurrence rates up to 15-25% in very and extremely premature infants (<32 and <28 weeks of pregnancy) (Poryo et al., 2018). Cerebral hemorrhages are among some of the causes of seizures, where both cerebral hemorrhages and seizures are deteriorations associated with poor neurological outcome, mortality and other unfavorable outcomes in newborns development (Luca Cattani et al., 2017; Facini et al., 2016; Huntsman et al., 2008; Lee et al., 2012; Poryo et al., 2018; Watson, 2010; Whitelaw & Lee-Kelland, 2017; Zupanc, 2004).

Cerebral hemorrhages are often caused by the absence of autoregulation (ability to maintain cerebral blood flow despite changes in cerebral perfusion pressure) in preterm infants (Elser et al., 2011). There is no (full-time available) real-time measure to identify infants with impaired autoregulation, which is why IVHs are commonly discovered with a head ultrasound or magnetic resonance imaging (MRI), to detect whether neurological damage has occurred (Elser et al., 2011). Studies have expressed the need to reduce mortality and the burden of disability that arises from conditions in relation to cerebral hemorrhages (Whitelaw & Lee-Kelland, 2017). For instance, the meta-analysis of Whitelaw & Lee-Kelland (2017) attempted to change treatment methods in order to reduce complications post-hemorrhage. Researchers are exploring non-invasive methods to monitor autoregulation ability (e.g. Cerebral Oximetry[10]) (Elser et al., 2011), and hence, to detect infants at high risk of hemorrhage and act accordingly (potentially before breakout). Nevertheless, there is a lack of research on early detection methods of cerebral hemorrhages in infants.

3.4.2 Movement patterns associated with (severe) cerebral hemorrhages

Despite the unclear descriptions of cerebral hemorrhage symptoms, some clinical warning signs are expressed, most specifically related to seizures. Around 7-18% of neonatal seizures are caused by intracerebral hemorrhages, where a tonic extension or flexion of limbs often signals severe intraventricular hemorrhage in preterm infants, including decerebrate[11] or decorticate[12] posturing (Facini

[8] The functional tissue of an organ as distinguished from the connective and supporting tissue
[9] A group of permanent movement disorders, explained in section 11.2.1.
[10] Non-invasive, continuous monitoring of cerebral oxygenation.
[11] hyperextension of the upper and lower extremities
[12] hyperextension of the lower extremities and tonic flexion of the upper extremities (and sometimes with axial hyperextension)

et al., 2016; Sankar et al., 2008; Zupanc, 2004). Other recognized symptoms include apneas, muscular twitches, and convulsions (Zupanc, 2004).

3.5 Seizures

3.5.1 Clinical event description and impact

A seizure is a sudden, uncontrolled, electrical disturbance in the brain (Chatterjee, 2011; Facini et al., 2016), often defined as paroxysmal alterations of the neurological function e.g. behavioral, motor or autonomic function (Luca Cattani et al., 2017; Sankar et al., 2008; Zupanc, 2004). Seizures are the most common symptoms signaling underlying neurological disease, as it represents a distinctive symptom of abnormalities. The developing brain is highly susceptible to neurological problems, frequently accompanied/exhibited by neonatal seizures (Zupanc, 2004). Most neonatal seizures occur during the first year of life (usually in the first 3 days of life), risking permanent changes in the central nervous system (CNS) with long-term neurodevelopmental consequences (Facini et al., 2016; Zupanc, 2004). Seizures are strongly related to cerebral hemorrhages and other brain deficits, the most common cause being hypoxic-ischemic encephalopathy (40-65%) also known as perinatal asphyxia[13] (Luca Cattani et al., 2017; Facini et al., 2016; Sankar et al., 2008; Zupanc, 2004). Furthermore, 18-25% of patients with (a history of) neonatal seizures have shown to develop epilepsy (Facini et al., 2016; Van den Bruel et al., 2010; Zupanc, 2004). Other common etiologies are meningitis, cerebral palsy, and sepsis (Luca Cattani et al., 2017; Facini et al., 2016; Rosenberg et al., 2010; Sankar et al., 2008; Zupanc, 2004). Assessing seizure onset often assist in determining the cause of the seizure, as seizures occurring day 0-3 of life have a higher chance of being related to perinatal asphyxia, intracranial hemorrhage, and metabolic defects, while day 4-7 to sepsis, meningitis, and metabolic causes (Sankar et al., 2008).

A recognized issue in NICUs is the unobvious distinction of seizures and tremors (non-epileptic motor phenomena, which are described in detail below) that risk negative effects of under-treatment of seizures, or overtreatment of non-epileptic events (Facini et al., 2016; Karayiannis et al., 2006; Orivoli et al., 2015; Zupanc, 2004). The underlying cause of benign tremors often differs from those that cause seizures, requiring a different treatment approach (Huntsman et al., 2008). In addition, standard anticonvulsants[14] have potentially harmful side effects e.g. bradycardia, respiratory depression[15] or further brain injury, and should be avoided when possible (Huntsman et al., 2008). For the reasons expressed above, timely recognition and correct diagnosis of seizures are important to differentiate epileptic seizures from other events (Facini et al., 2016; Karayiannis et al., 2006), to initiate antiepileptic therapy and detect etiology as it impacts prognosis (Luca Cattani et al., 2017; Zupanc, 2004).

The current golden standard for detecting seizures is by a continuous electroencephalogram (EEG) recording. This is unideal, as most infants are not continuously monitored by EEG, and not all seizures have a correlating EEG component (Facini et al., 2016; Zupanc, 2004). Seizure detection by a video camera is often used (Karayiannis et al., 2006), initially focusing on observational classifications of seizures (Cabon et al., 2019). The development of video processing increased the number of approaches for automatically detecting/classifying seizures based on motion descriptors, however, this method has some efficiency

[13] A medical condition where deprivation of oxygen (during birth) last long enough to cause physical harm to the infant (usually the brain).
[14] Anti-epileptic medication
[15] Slow and ineffective breathing

constrictions as it (currently) requires a person to observe the camera in real-time (Karayiannis et al., 2006). Consequently, other unobtrusive methods for effectively detecting seizures are desired.

3.5.2 Movements associated with seizures

Seizures are often associated with global (whole body) movements, local movements, or more subtle movements (Chatterjee, 2011; Facini et al., 2016). Various seizure types exist, and recognition of seizure type is important for detecting underlying etiology, as different seizure types are characterized by different behavioral and motor manifestations (Luca Cattani et al., 2017; Facini et al., 2016; Joshi et al., 2018; Sankar et al., 2008; Zupanc, 2004). The most common seizure types are briefly discussed in this section. A summary of the specific movement patterns marked in blue for each seizure type is shown in Table 4 in section 10.4 in Appendix C, whereas the general movement patterns are summarized in the encoding matrix in Table 1.

Subtle seizures constitute to around 50% of all seizures in infants and are frequently missed due to the mild clinical manifestations of ocular movements, oral movements and stereotypic limb movements e.g. bicycling movements, and a tonic posture of a limb (Facini et al., 2016; Sankar et al., 2008; Zupanc, 2004). Tonic seizures resemble decerebrate or decorticate posturing occurring in neonates with abnormal neurological functioning, and are typically associated with apneas (Huntsman et al., 2008; Sankar et al., 2008). Myoclonic seizures are brief, shock-like jerks of a muscle or a muscle group, associated with lightning-fast jerks of extremities (upper extremities more than lower) (Sankar et al., 2008). Myoclonic seizures have the worst prognosis for neurodevelopmental outcome or seizure recurrence (Sankar et al., 2008), as it may signify epilepsy[16], exaggerated physiological myoclonus of sleep or neurological injury (Facini et al., 2016; Zupanc, 2004).

Tonic and myoclonic seizures are sometimes referred to as spasms, consisting of movements with "episodes of shoulder and/or limb stiffening, occurring frequently in short clusters ranging from a minimal elevation of the shoulders while moving the head downward to a more sustained tonic contraction" (Fernández-Alvarez, 2015). Another term is myoclonus, described as "a sudden, brief, shock-like involuntary movement" (Mercolini et al., 2015), or "spasmodic jerky contraction of groups of muscles" (Fernández-Alvarez, 2015). Myoclonus is either localized, or generalized (whole-body), and can be single or repetitive (Huntsman et al., 2008). A short span of spasms/myoclonus, while having more rapid jerks, the absence of slow return and a predilection for flexor muscle groups distinguishes them from clonic seizures (Chatterjee, 2011; Sankar et al., 2008).

Clonic seizures are the type of seizures associated with convulsions and twitches of facial, limb, or axial muscles (Zupanc, 2004). Convulsions are classified as repetitive, stereotyped non-suppressible motor movements (Singh et al., 2003). Convulsions are described as rapid and repeated contractions/relaxations of the muscles showing a sustained, rhythmical jerking or sudden, periodic and involuntary (violent and irregular) movements of limbs, with flexion/extension phases that are different in amplitude (Chatterjee, 2011; Collins & Young, 2017; Facini et al., 2016; Huntsman et al., 2008; Orivoli et al., 2015; Zupanc, 2004).

[16] A neurological disorder in which brain activity becomed abnormal, causing seizures/periods of unusual behavior/sensations/loss of awareness.

In addition, convulsions are associated with ocular phenomena, movements involving the jaw and the extremities, and autonomic signs e.g. HR increase, hypertension[17], and apnea (Huntsman et al., 2008).

Seizures that involves convulsionary movement patterns are important to detect to assess underlying pathology, as it often relates to meningitis[18] and (severe) cerebral hemorrhages (Huntsman et al., 2008; Orivoli et al., 2015; Weber et al., 2003). Convulsions that persist/exacerbate/exaggerate often increase suspicion of serious diagnosis (Collins & Young, 2017). One challenge of detecting the seizures involving convulsions is the similarities of the movements related to pathophysiological seizures, and the movements related to benign tremors (Facini et al., 2016; Orivoli et al., 2015; Sankar et al., 2008).

Benign (fine) tremors are the most common paroxysmal motor phenomena (abnormal movement) seen in infants and are frequently reported during the first days of life in healthy newborns (Facini et al., 2016; Huntsman et al., 2008; Orivoli et al., 2015). Fine tremors are defined as an involuntary, rhythmical oscillatory movement of equal amplitude around a fixed axis (Collins & Young, 2017; Huntsman et al., 2008; Orivoli et al., 2015). Sankar et al. (2008) define tremors fragmentary myoclonic jerks, being fast movements (4-6 per sec), with the absence of a fast and slow component. Fine tremors primarily involve the head, arms, shoulders, and occasionally, only the trunk, but can also be seen as very small movements, e.g. a familial trembling of the chin (Orivoli et al., 2015). Fine tremors are not considered seizure predictors, even though the movement pattern relates to other clinical events presented in this paper.

Convulsions differ from (benign) tremors as it is irregular and arrhythmic (Huntsman et al., 2008). Furthermore, benign tremors and convulsions are usually distinguished based on quality, frequency, amplitude, and degree or repetitiveness of the movements (Basheer, 2015; Huntsman et al., 2008; Orivoli et al., 2015). Benign tremors typically have a high frequency (>6 cycles per second (Hz)) as compared to low and varying frequency for convulsions (<6 cycles per second(Hz)), and low amplitude (<3 cm, 8-10Hz) compared to high and varying amplitude for convulsions (>3cm) (Basheer, 2015; Fernández-Alvarez, 2015; Huntsman et al., 2008; Orivoli et al., 2015). Other characteristics are whether the movements are symmetrical, fine, and can be stopped with stimulation (fine tremors) or whether they are irregular and jerky, and cannot be stopped (convulsions) (Fernández-Alvarez, 2015; Huntsman et al., 2008; Orivoli et al., 2015; Sankar et al., 2008). In addition, fine tremors are not associated with eye movements, autonomic changes or EEG correlates (Sankar et al., 2008).

3.6 Pain

3.6.1 Clinical event description and impact

The focus of modern technology has shifted from solely keeping the infant alive to strategies of improving quality of life, which includes reducing the detrimental effects of procedural pain and discomfort (Chen et al., 2012). NICU infants experience several painful procedures during their early life, e.g. obvious necessities of inserting intravenous catheters and blood tests, detachment of electrodes, and more, with little recovery time between painful events (Chen et al., 2012; De Clifford-Faugère et al., 2017; L. Holsti, 2004; Stevens et al., 2014). Many infants do not receive adequate treatment during painful procedures, and unmanaged pain has several immediate and long-term consequences (Castral et al., 2008). First, pain affects infants' health and development (L. Holsti, 2004). Early exposure to pain may have long-term

[17] High blood pressure
[18] Infection or inflammation of the meninges

effects on the brain structure and functioning in preterm infants (Peyrovi et al., 2014), as it alters nociceptive pathways[19] that persist after NICU discharge (Liisa Holsti et al., 2005; Stevens et al., 2014). Immediate consequences of pain include alterations in hemodynamic stability and altered stress hormone expression, whereas cumulative pain is a contributing factor of impaired visual, cognitive and motor development (Chen et al., 2012). Second, pain impairs the ability of the infant to successfully attend and learn from the external environment (Watson, 2010). These behaviors, in turn, interfere with caregivers' ability to correctly translate emotional cues and respond appropriately, quickly and consistently to their needs (Watson, 2010). Third, failure to recognize pain can have detrimental consequences e.g. physiological and behavioral changes, whereas faulty recognition of pain often results in an improper use of sedatives or analgesics (De Clifford-Faugère et al., 2017). Accurate interpretation of pain and appropriate administration of analgesics and other sedatives is important to prevent long-term side effects of opioid use, as analgesics may act differently in the brain depending on the presence or absence of pain (Liisa Holsti et al., 2005). Therefore, relieving and detecting pain is important to detect health deteriorations, and to improve health outcomes (Hill et al., 2005; Peyrovi et al., 2014).

3.6.2 Movement patterns associated with pain

Pain management currently relies on scoring systems. Among others, these scoring systems are based on movement observations, as body movements contain important information about infants' responses to painful events (Liisa Holsti et al., 2005). Neonatal Infant Pain Scale (NIPS) scores facial expression and movements of arms and legs (Hill et al., 2005; Peyrovi et al., 2014). Premature infant pain profile (PIPP) has been widely used to measure pain, and contain indicators such as brow bulge, eye squeeze, and nasolabial furrow during painful stimulus (Stevens et al., 2014). ComfortNeo is a procedure of approximately 5 minutes measuring pain/distress/comfort, with indicators such as alertness, body movement, and facial movement. Newborn Individualized Developmental Care and Assessment Program (NIDCAP) formulates a personal plan of care based on observations of infants' behavioral cues, by building on infants' strengths and supporting the areas of vulnerability (Als, 2009; L. Holsti, 2004).

NIDCAP assesses infant responses including motor behaviors and state organizational behaviors two minutes before, during, and after a procedure (L. Holsti, 2004). Holsti (2004) found 8 of the sensitive NIDCAP infant behavior movements to be associated with pain (and valuable for identifying pain) in preterm infants, including several discrete body movements. Finger splay (move fingers out and apart) may be a developmentally specific distress cue (L. Holsti, 2004). This cue is seen more often in younger infants <30 weeks compared to older infants (both during painful procedures and during baseline measures), suggesting that preterm infants are relatively more stressed (L. Holsti, 2004). Fisting is another considered pain indicator, and like finger splay, fisting is shown more in infants <30 weeks of age (L. Holsti, 2004). "Hand on face" is a defense-like action possibly representing an additional pain cue for preterm infants, serving as a protective action interpreted as an attempt to create a barrier between the face and the stimulus (Liisa Holsti et al., 2005). Flexion/extension of the extremities is reported and assessed as indicating pain in other studies, with emphasis on lower limb extension as a consistently observed distressed cue (L. Holsti, 2004). Flexor actions of the legs is explained as possible reflex responses to pain and tactile stimulation in preterm infants (Liisa Holsti et al., 2005). Tongue extension has been reported as a marker of pain response in preterm infants, although it is unclear whether this sign is perceived as pain or as a general indicator of stress (Liisa Holsti et al., 2005).

[19] pathways relating to the sensation of pain (e.g. pain reactivity)

Morison et al. (2003) investigated the stress cues from the NIDCAP model where they analyzed preterm infants pain-reactions after lance (heel prick), and they found extension of arms and legs (80% of the infants) and finger splay (70%) to be most common, and hence promising as clinical pain indicators for preterm infants (in addition to facial and physiological pain measures). Furthermore, 70% showed flexed arms and legs, while they also found that 70% of the infants had a lower incidence of twitches and startles compared to baseline. This is in line with findings from Grunau et al. (2000), who did not observe tremors, startles, twitches, or arching of the back during painful procedures, however, opposed to the findings of Holsti et al. (2005). Other findings of behavior occurring during pain, included airplaning[20] (30%), sitting on air[21] (30%), hand on face (30%), hand to mouth (30%), clasping (grasping) (20%) and saluting[22] (20%). Arching, squirming, tongue extension, and tremors were infrequently observed responses (all behaviors: 10%) (Morison et al., 2003). Their findings are shown in section 10.4 in Appendix A.

Hence, motor behaviors (including posture) and movements patterns, particularly in the face, are important indicators for pain and stress in infants (Hill et al., 2005; Liisa Holsti et al., 2005). In fact, facial activity changes/grimace is considered to be the most consistent and convincing indicators or pain (and stress), with a greater number of brow bulge during pain compared to stress (Liisa Holsti et al., 2005). Typical facial expressions of pain are captured in the Neonatal Facial Coding System (NFCS) (Morison et al., 2003), and by PIPP. For example, brow bulge, eye squeeze, and nasolabial furrow are classified by PIPP as Maximum (more than 70% of the time), moderate (40-69%), minimum (10-39%). Other factors involve, for example, wide-open mouth (Hill et al., 2005).

3.7 Stress/Discomfort

3.7.1 Clinical event description and impact

Stress and discomfort in infants are behavior indicating that they are neither comfortable, nor experiencing pain, but rather that something is disturbing the infants. Increased stress that is undetected/untreated may have lifelong consequences including cognitive disorders, learning disorders, poor motor performance, psychosocial disorders, impulsive behavior, and lack of control in social situations (Hill et al., 2005). In addition, acute, significant stress may lead to hypertension and respiratory compromise, including significantly increased morbidity and mortality in the preterm population (Newnam & Parrott, 2013). This is a result of preterm infants' adrenal insufficiency due to immature adrenal glands, in which preterm infants require replacement of cortisol during stress (Newnam & Parrott, 2013).

3.7.2 Movement patterns associated with stress/discomfort

Behavior during pain and stress is not obviously distinguished in literature, and there is a lot of overlap (of which most of the pain cues are often related to stress as well). Therefore, several patterns mentioned for stress and pain in the previous section are included in the encoding matrix.

State and behavioral changes such as shutting out the environment, dull/sleep states, unfocussed or uncoordinated eyes, limp arms and legs, and facial movements such as yawning are all associations to stress defined by Brazelton (1984). These signs either indicate stress in ill infants, or infants recovering

[20] Extending the arms laterally

[21] An action whereby the legs are flexed at the hips and extended at the knees

[22] Stretching hands upwards. A detailed explanation is found in section 12.2 in Appendix C.

from stress/immaturity (Brazelton, 1984). Holsti (2005) associates extensor movements of arms and legs, finger splay, airplane, sitting on air and salute as predominant movements of stress. Furthermore, tremulousness and startles are mentioned (Ohgi et al., 2003), and excessive sucking movements (without anything in the mouth to suck on) (Chatterjee, 2011). Another important indicator of stress (and possibly pain) is when infants move out of the fetal posture. HCPs facilitate a fetal posture in infants by the use of a "tucking mechanism" that aid postural security by the positioning of the four limbs in a semi-flexed posture to limit environmental stimuli (Hill et al., 2005; Zahed et al., 2015). This postural security is important, as preterm infants have decreased ability to maintain physiological flexion independently (Hill et al., 2005). Bent joints promote normal motor development as it allows for muscle, tendon and bone structures to develop more harmoniously, and aid in energy conservation (Hill et al., 2005; Zahed et al., 2015). Positioning infants in a fetal posture enables them to move towards and across the midline (healthy movements) which helps infants to use self-regulation skills and abilities (e.g. hand-to-mouth, grasping, holding) to cope with, and reduce pain and stress (Hill et al., 2005; Zahed et al., 2015). Furthermore, it assists in preventing frozen flexion or (hyper)extension postures and head rotation movements or to reduce abrupt movements of the limbs (Zahed et al., 2015). Placing infants in the fetal posture can help in adjusting the quick response of the autonomic nervous system such as increased heart rate (Peyrovi et al., 2014). Most research describes the tucking mechanism as pain revealing strategies, as infants who repeatedly move out of the fetal posture is related to pain/discomfort, while disrupting development (Hill et al., 2005; Peyrovi et al., 2014).

4 METHOD – INTERVIEWS AND SURVEYS

4.1 INTERVIEWS

Participants

Interviews were restricted to HCPs who have some relation to the NICU. Participants were invited by email, sent out by a Philips employee to contacts within the NICU environment. Some participants were secondary selected via HCPs who participated in interviews in the early process.

Participants were 21 HCPs (14 NICU nurses, 6 neonatologists, 1 nurse practitioner) who participated in the 18 interviews conducted (one interview with 2 nurses together, and one interview with 2 neonatologists and one nurse together). Participants were from hospitals in four different cities in the Netherlands, one in Norway, and one in Australia. The majority of the participants (13) worked at Maxima Medisch Centrum in the Netherlands, while the rest worked at Utrecht Medisch Centrum (1), Amsterdam Medisch Centrum (2), University Medical Center in Groningen (3), Ulleval Sykehus in Oslo, Norway (2), and Westmead children's hospital in Australia (1). 12 participants had more than 10 years of experience in the NICU, 6 had 5-10 years of experience in the NICU, and 3 had 2-5 years of experience in the NICU. Participants were required to sufficiently understand and speak English or Norwegian, and participation in this study was on a voluntary basis. Participants provided verbal consent to participate in the interviews.

Materials

A Marantz PMD620 recorder was used to record the interviews for transcription purposes.

Design and procedure

Semi-structured interviews were conducted first and foremost to gather information about infant motion in relation to the different clinical events recognized in the literature. Second, participants were asked (freely) to express which clinical event areas they consider important for the implementation of motion-tracking technology in NICUs. This was asked to check whether the recognized clinical events from the literature were also considered the most important clinical events by the interviewees, whether some were less important, and whether some clinical events that were not included in the encoding matrix from the literature should have been included. Third, HCPs were asked to express potential use-cases, in particular, which assistance they expected from motion-tracking technology in the NICU in the future, to improve their experience of providing nursing care.

Therefore, an interview guide was created based on a mix of open-ended questions about HCP's general opinion about motion-tracking technology, and more specific questions about the movement patterns and clinical events recognized in the literature. The interview guide is shown in section 0 in Appendix E. The goal was to collect new or additional knowledge to clinical events/movement patterns not obviously clear in the literature. Due to the semi-structured interview approach, the interview guide was meant as a guideline, rather than a "strictly follow" procedure. Consequently, the focus of the interviews differed per person, depending on their interest and area of expertise. The interview guide (and the details about the study) were submitted to an internal ethics, regulation and privacy review of Philips (ICBE). This (iterative) process involves qualified personnel reviewing the study and providing feedback, before approving the study. After approval, the interview requests were sent to participants. Participants who expressed willingness to participate in an interview of 45 minutes received an information letter and were informed of their rights in a privacy notice (adapted to fit the study from a template from Philips) by email. Following this, interviews were scheduled at participants' preferred time and place. The interviews mostly occurred at the hospital where the participants worked, either in a cafeteria space or in a closed office. The interviews were initialized by an explanation of the purpose of the study and a short summary of the participants' privacy rights. After receiving verbal consent of participation (including verbal consent of the interview being recorded for transcription purposes), the interview was conducted.

Interview analysis

After transcribing the interviews, two approaches were used for analysis, namely a thematic analysis approach and a narrative analysis approach. The primary objective was to select information for the encoding scheme. The aim of the thematic content analysis was to find common movement patterns across the data set of transcribed interviews. This process was initiated by highlighting all the relations between movement patterns and clinical events in all the interviews. All of these relations were then sorted per clinical event, and compared to the encoding matrix from the literature. If the movement patterns (rows) from the interviews did not fit to an existing row, the explanations from HCPs were re-inspected to assess whether they were similar to definitions from the literature. If the explanation was not similar to any existing row, a new row of this movement pattern was created. After filling in the movement patterns, the rows were checked, and some rows were merged if they expressed the same movement patterns. This process created an updated frame of the encoding matrix based on both literature and interviews, by adding all the new rows of movement patterns mentioned by any HCP if they were not present in the encoding matrix from the literature. New columns of clinical events were only included if they were considered as important by more than 3 participants and if they were not too similar to the clinical events selected from the literature. Once the updated frame of the new encoding matrix was created, relevant information from the interviews was added to the appropriate cells.

The narrative analysis was conducted as a secondary step, where each interview was analyzed individually. This was done to discover new insights and meanings; either to complement possible information missed with the previous approach or to gather more details for the already selected clinical events/movement patterns from the literature review. This method enabled the detection of comparisons and contrasts between the different interviews, and the search for connections and different interpretations while getting an idea about what is important for the HCPs.

During the interview analysis, the participant number of each participant who mentioned the movement pattern for each clinical event was tracked, in order to have an overview of how many people mentioned the association. This allowed for using both a qualitative approach (recognition of important movement patterns for each clinical event) and a quantitative approach (which movement patterns and clinical events were mentioned more often with potential confounds). An important mark for the quantitative approach, however, is that not all interviews contained the same questions. Therefore, the number of times some movement patterns or clinical events were mentioned does not directly mean that it is more/less important. Nevertheless, this information could still suggest what is obvious/clear to HCPs, and what still needs further research.

The interview analysis resulted in an overview of all the clinical events mentioned, movement patterns related to each clinical event, and a document with relevant quotes. In addition, it resulted in an overview of all use-cases mentioned in the interviews. Following the interview analysis, an investigation of whether the newly collected information not yet available in the previous version of the encoding matrix was present in literature (to the best of my knowledge). Lastly, the encoding matrix was modified to include both information from the literature and from the interviews.

4.2 SURVEY

Design

The surveys served to validate the information in those cells of the encoding matrix (as generated by literature review and interviews), which were not suggested by two or more papers in the literature. Therefore, the focus was on non-empty cells that had information from interviews, but were unclear/absent in the literature. As there were still too many of these cells to include in the survey, the selection was narrowed down by selecting only cells that were mentioned either by three or more participants, or suggested in the literature (by one paper), and mentioned by two or more participants. In addition, it was occasionally chosen to include a cell mentioned by only one participant (or by none) if it was either convenient to add or because the cell was considered important for another reason. Some cells that contained more than two articles for the clinical event discomfort were excluded, due to the lacking differentiation from pain. This was compensated by adding an open-ended question about the differences of movements in relation to pain and to discomfort. Lastly, some of the cells of which there was already proof in literature were included in the survey to test the validity of the survey responses.

Participants

Because the survey was in English, participants were required to have a sufficient understanding of English. Participants were recruited from all over the world, and invited by email. These emails contained a link to the survey and were sent to known contacts (HCPs with relation to the NICU) of Philips Research, with a request to fill it in and to pass it on to other communities within neonatal care. Participation in this study was on a voluntary basis.

Participants were 47 HCPs (33 participants completed the survey, and 14 participants partially completed the survey). The independence of different questions allowed for the inclusion of the data from the partially completed surveys in the analysis. 13 additional participants only filled out background information and were excluded from further analysis.

Participants who completed the survey were 33 HCPs (14 NICU nurses, 10 neonatologists, 3 nurse practitioners, 1 neonatal therapist, 1 occupational therapist, 2 NIDCAP professionals 1 physiotherapist/NIDCAP professional and 1 other (non-specified)). Participants who partially completed the survey were 14 HCPs (11 NICU nurses, 1 neonatologist, 1 occupational therapist, 1 physiotherapist). The participants worked in Qatar (N=12), The Netherlands (N=9), Belgium (N=9), United States (N=5), Australia (N=3), United Kingdom (N=2), Portugal (N=2), Sweden (N=1), Italy (N=1), Israel (N=1), Germany (N=1), and Norway (N=1). The majority of participants had more than 10 years of experience (N=37), whereas some had 5-10 years of experience (N=7) and 2-5 years of experience (N=3).

Materials / Measures

The survey was hosted in the enterprise feedback management (EFM) tool by VERINT licensed by Philips. The data was analyzed in IBM SPSS Statistics 23.0.0.0 x64. The survey consisted of 16 questions, designed as a mix of qualitative (open-ended) and various types of quantitative (close-ended) questions, as it is more compelling for respondents to answer different types of questions. The survey questions are shown in Section 15, Appendix F.

Quantitative questions

5-point Likert scales were used to assess respondents' level of agreement/occurrence of infant posture (Q1) and extension of extremities (Q2) in relation to different clinical events. These two questions were included because several HCPs suggested a possible relation between these two and several clinical events. The literature suggests a relation between "repeatedly moving out of fetal posture" and discomfort or pain, although not directly clear. This is valuable to assess the relationship from the perspective of the movement pattern e.g. what is the implication of infants moving out of fetal posture, rather than anchoring participants to each clinical event before asking the question.

5-point Likert scales were used from the perspective of anchoring participants to cerebral hemorrhages (Q10) and necrotizing enterocolitis (NEC) (Q11), as there was a lack of clarity for several of these movement patterns during the interviews. In addition, including these as separate questions enables the testing of several movement patterns simultaneously, which was valuable for these clinical events.

6-point scales were used to assess the speed of movements of infants in pain (Q7), as there was a suggestion of infants in pain moving faster than normal. This scale used 6 options, as the inclusion of "no movement" was considered in addition to the other categories. This was done to not force participants to answer that infants typically show movements all the time.

"Choose many" questions were added for movement patterns in relation to pain (Q6) and movement patterns in relation to (severe) cerebral hemorrhages (Q9), as there were several movement patterns suggested for these clinical events, though not proven. This question enabled the inclusion of various movement patterns in one question.

When assessing activity level (Q4), a multiple-choice matrix was used following the advice from a pilot-participant who specified that some clinical events might have several associated activity level signatures. Locking participants to one answer might reduce the quality of the outcome, as participants would be forced to choose.

A multiple-choice question of movement amplitude (Q13) and specific movement patterns (Q5) was asked to test whether there were some dominant categories for the selected clinical events. These questions included an option of "other" to give participants the chance not to have an opinion about this. The "choose many" questions were included to check whether the (many) movement patterns suggested for pain and cerebral hemorrhages were also recognized by other HCPs

The yes for (other)/no question about the presence of lower limb movement (Q3) was asked to test the lack of clarity of whether there is value in monitoring lower limbs apart from upper limbs, whereas the yes for/explain/no question for alarms (Q14) was asked based on specific interest from Philips. Lastly, a rank order question with ties aimed to detect which use-cases were most attractive to HCPs (Q15).

Qualitative questions

The open-ended question about movements distinguishing discomfort from pain (Q8) was asked because they had similar predictive signs in the literature and in the interviews. Due to the explorative nature of this research, participants were asked for additional remarks (Q16) in order to collect additional information that might have been missed during the literature study or during the interviews.

Procedure

The EFM tool automatically generated a link to the survey. Participants received the link to the survey via the internet (email), where they were directed to the information page with a summary of a privacy notice. They had the option to either read the full notice or start the survey. The first questions of the survey asked for background information, containing a question about their profession, years of experience (in a range) and which country they work in. Then they were directed to the survey, where they had to answer 16 (mandatory) questions about infant movement in relation to some chosen clinical events. All answers up until submitting were saved.

Analysis

The dataset was first imported to SPSS. Respondents without some relation to the NICU were omitted. Likert items anchored with consecutive integers (1=" Strongly disagree" to 5= "Strongly agree") were reversed if needed, such that a high number indicated strong agreement. The data was checked for normality with Shapiro-Wilk tests (when applicable). For the analysis, descriptive statistics were used to analyze central tendency (mean, median and mode), and variability of frequency (percentage) showing the most common/average responses. As the surveys were used for validation, the hypothesis of whether there exists a relation between specific clinical events and posture/activity level/movement patterns was tested for each question.

The Likert item questions (Q1, Q2, Q10 and Q11) were considered as interval data, and tested with one-sample t-tests, comparing the data to the neutral middle of 3. Q7 and Q15 were analyzed in a similar way, although these had different scoring elements, in which Q7 score on the speed of movement, and Q15 score on the ranking of opinion for different clinical events. One exception of the analysis approach is for the 6 point scale of Q7, in which it was compared to the neutral response 4 (as 1 was an addition of no movement at all). For acceptance in the encoding matrix, it was necessary for these questions to have the standard 5% significance chance on the one-sample t-tests looking for a difference of the mean from the neural value 3 of the scale.

Questions Q4, Q5, Q6, Q9 and Q13 on categorical ordinal data was firstly analyzed with univariate analysis by using the central tendency statistics of mode and median, and frequency distributions. Second, these questions were then checked by the Wilson confidence interval as calculated by using "Epitools[23]" which summarized categorical or continuous data. The full confidence intervals above 50% were considered as the majority of experts agreeing to this movement patterns as a relation to a clinical event. There is no appropriate threshold defined in literature, in which a threshold of 50% was selected as it requires the majority of the participants to have the same opinion about a presence of a specific movement pattern for a specific clinical event, which seems appropriate as the population of participants consist of experts in the field. Therefore, only the relations of movement patterns to a clinical event that had the full confidence intervals above 50% were significant and included in the final encoding matrix.

As a remark, even though the nature of Q4 about infants' activity level is in a similar fashion as the Likert scale questions, a t-test was not applicable as respondents could select multiple answers for each

[23] https://epitools.ausvet.com.au/ciproportion

question. Conducting a t-test on this would require splitting up responses of participants who selected several options.

Q3, Q12, and Q14 were a mix of categorical ordinal questions, and open-ended. These questions were analyzed by both frequency distributions and qualitative analysis. For the qualitative analysis, the information was coded into a layer diagram (sorted by the content of the quote), in which content analysis was used to summarize the statements. This qualitative analysis approach was also used for the open-ended questions (Q8 and Q16).

5 Results – Interviews

This section presents the results of the interview analysis for each clinical event. Based on this analysis, the encoding matrix in Table 1 was modified by the information from the interview analysis, which is shown in Table 2. The modified matrix includes the results of the literature review and a summary of the interview analysis. The number of participants from the interviews who mentioned each relation is presented in the cells, whereas some additional rows are included based on new information. These additional rows are first dynamics of movement (continuous, short sharp bursts or episodic). Second, head extension and head bobbing was added (head bobbing was added to the same cell as moving head downward) as it was mentioned by some HCPs as possible predictors for term infants. Third, "Stretch/drown" was included, as HCPs expressed infants' inability to get out of an extension, and hence, show struggling movements while extending the extremities. These newly added rows were again cross-checked with literature. One new clinical event area (meningitis) was mentioned in some interviews, although not included as a new column in the modified encoding matrix. This was first because it was not mentioned as the most important clinical event, and secondly because it closely resembles movement patterns in relation to another clinical event (sepsis). Therefore, it could serve as secondary benefits of future disease detection algorithms, although the details for this implementation are above the scope of the current paper.

The subsequent sections describe each clinical event and the related movement patterns from the interviews, and similar to the previous section, the movement patterns are marked in blue. Similar to the literature review, the interviews related to the clinical events sleep-wake and neurodevelopment are described in section 11.1.3 and 11.2.3 in Appendix B. The interviews also yielded valuable insights into how tracking of movement patterns could be relevant for specific use-cases (related to the clinical events). These use-cases are compiled in Appendix D. For the interested reader, the vital signs associated with each clinical event can be found in section 12.3 in Appendix C.

Table 2: Encoding matrix after the interviews. The black numbers in the cells depict how many interviews mentioned the relation. The red numbers illustrate the article codes supporting the relation from the literature review, and the list of the articles related to each red (and blue) number can be found in Table 8 in section 12.1 in Appendix C. The lighter shaded blue cells were mentioned by 2 or more papers, and are clear from the literature. The darker shaded blue cells are not mentioned in the literature but suggested by 3 or more interviewees, or relations that are sometimes mentioned in the literature (1 paper) and suggested by 2 or more interviewees. Cells that contain an asterisk are included in the survey, for reasons to be described in the next section. Detailed explanations of the rows are found in section 12.2, Appendix C.

Supported in the literature | Mentioned by 3 or more interviewees or one paper and 2 or more interviewees

Clinical event / Posture	Discomfort / stress	Pain	Sepsis	NEC	Cerebral hemorrhage	Seizure	Apnea
(Repeatedly move) out of fetal position	8, L33, L34 *	2, L33, L34 *	2 *	3 *	2 *		
Overall activity level (gross body movement)							
Increase / active	9 *	10, L5 *	4, L14 *	8 *	10 *	2 *	
Lethargy	3 *	6 *	18, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16 *	12, L17 *	6 *	*	

Movement patterns							
Abnormal movement pattern (different movements from normal)			1		3 *		6, L21, L24, L31 (struggling/thrashing)
"Dynamics" of movement							
Continuous	1	4 *			1	*	*
Sharp (short)		*				*	3 *
Episodic: ca few times per hour, each lasting 10-20 seconds (ca)		*				2 *	*
Cramps/tremor/ tremulousness	2, L3, L36	3, L36 *		1 *			
Convulsions			4, L7, L8, L10, L11, L13, L14, L15, L20 (term)		7, L9 *	16, L2, L8, L9, L21, L22, L30	
Startles (shock, repeating)	1, L3, L36	1, L37 (L35, L36 decrease) *				1	
Twitches	L36 (extremities)	L37 (L35, L36 decrease) (extremities) *			L9	L9	
Head/Neck							
Head extension	3				1 *		
Bobbing (up and down) / moving downward					1 *	1, L19	
Face							
Grimace	5, L4, L37	12, L5, L33, L34, L35, L36, L37, L26 *			3 *		1
Repetitive face movements	1, L1, L2	1, L34, L37, ComfortNeo				2, L9, L21, L22, L30	
Tongue extension	L37	L36, L37 *					
Specific eye movements	1, L1, 37	L37 *				2, L2, L21	
Torso/trunk							
Diffuse squirm /wriggling the torso	4, L36	4, L36 *		1 *		1	
Absence of thoracic movement (up and down) (absence of periodic breathing movement)							6, L9, L21, L24, L31
Arching of the back	L36	L36 *					
Limbs							
Absence of periodic breathing movement							L9, L21, L22, L24
Jerky movements						L2, L20, L19	
Extension of limbs	9, L36,L37 *	5, L5, L36 *	2, L13 *	3 *	3, L9, L20, L21 (decerebrate posturing) *	1, L9, L19, L20, L21, L28, L29 (decerebrate posturing) *	
Repetitive extension/flexion movements	3, L37	2, L5, L33 *		*	1	1, L2, L8, L9, L21, L22	
Stretch/drown	8	2 *			1 *		

Flexor movements	L37	L5 (arms) and legs (L36) *					
Speed of movement							
Slow	(1)	*				1, L20, L22	
Fast	3	6 *			3 *	1, L20, L23	
Low frequency of movements (<6 Hz)						L29, L19, L27, L32	
High frequency: >3 in a few minutes	1	1			1		
Movement amplitude							
Small range (<3 cm)	*	*	*	*	2 *	1	
Large range (>3cm)	8 *	6 *	2 *	3 *	3 *	L29, L19, L27, L32	
Hand/foot clasp	L36	L36					
Upper limbs							
Saluted – extension of arms into midair in front of infant. / Vertical movement in space	3, L4, L36, L37	2, L5, L36, L37	1	1 *	1 *		
Airplane – extends arms laterally	1, L36, L37	3, L36, L37	1			1	
Grasping /Pulling/grabbing (e.g. tubes/wires)	6, L36, L37	2, L36, L37 *			1		
Hands							
Hand on face / Hand to mouth	L36, L37	L36, L37					
Fisting	2 L4, L36	4 L5, L36		2 *	2 *	1	
Finger splay	3 L36, L37	4 L5,L35,L36					
Lower limbs							
Extension of lower limbs (specifically)		1, L5, L37 *		2 *	L9, L20, L21 (Decorticate posturing) *	L9, L19, L20, L21, L28, L29 (Decorticate posturing) *	
Repetitive flexion-extension movements of lower extremities	4, L37	4 *		3 *	1 *	1 *	
Sitting on air: full extension of legs into the air	1, L36, L37	L36, L37			1 *		

5.1 Sepsis and NEC

During the interviews, it was clear that sepsis and NEC have a number of predictive movement patterns in common. Therefore, this section first describes the common predictors, before going into detail for sepsis and NEC separately. In general, HCPs highlighted that behavior deviating from normal behavior currently arises strong suspicion of illness. These behavioral deviations involve changes in activity level, presence of pain, difficulties falling asleep/reaching deep sleep, and some mentioned movement patterns.

Firstly, the relative change in infants' activity level, either as lethargy, restlessness (agitation), or both, were found to be the most prominent indicators/early-warning signs of disease. Some HCPs expressed lethargy as an early sign preceding changes in vital signs/clinical events such as apneas, bradycardias, and hypotension. Others, however, believe that illness is always initiated by restlessness early in the disease course, followed by signs of lethargy as a secondary sign. They express that the shorter periods of agitation preceding lethargy might have been unnoticed, which could explain why many people claim that lethargy is the only sign. Other HCPs mentioned that both lethargy and restlessness are predictors, in which:

> *"Signs of sepsis could be either direction, more quiet, but also more agitated".*

Nevertheless, lethargy might be the most viable sign of illness, where the "degree of exhaustion" is often proportional to the chances of severe illness development. One nurse explained a lethargic infant as:

> *"The power goes down, they have open hands, and are hypotonic (limp). Most of the time you see a baby that is empty."*

Second, an infant is "stiff in the body" or has "stiff limbs" can be seen as a predictor of illness. The stiffness can be categorized in various ways, as mentioned by a nurse:

> *"Arms and legs could stretch out, but it could also be that the whole body is bent, that is not a good sign. That the head comes back and the body is like a banana, with legs sticking straight out. And arms down on the side that sticks straight out is never a good sign."*

This suggests extended extremities, although it could also resemble decerebrate/decorticate posturing.

Third, several HCPs often associate stressful/painful behavior that persists after comforting measures to illness, as that often implies that "the problem has not been removed".

Detection of these indicators varies between a short time span e.g. an hour, and a longer period e.g. over two days.

5.1.1 Sepsis

Even though HCPs were not able to describe the abnormalities in detail, many were convinced that septic infants "definitely have a different movement pattern than a baby who is normal". Furthermore, some HCPs associated movements related to pain with sepsis, whereas others did not agree with this association. In addition, convulsions were associated with sepsis for term infants, as expressed by a neonatologist:

> *"I think maybe if you look to term infants and you see a convulsion, then I would start antibiotics immediately. Because then an infection is a serious cause of the epileptic insult. But the preterm infants, no."*

Lastly, HCPs considered apneas to be stronger predictors to sepsis for term infants as compared to preterm infants, as apneas are more unusual for term infants.

> *"When the baby is already there for 5 days, and then it starts getting apneas or bradycardias, then you can consider sepsis. Because after 5 days, if it was only apneas because of the immaturity of brain development, it should have started earlier."*

5.1.2 NEC

HCPs expressed some distinguishing predictors of NEC and sepsis, the most obvious one being that pain and agitation are recognized to a higher extent with NEC as compared to sepsis, whereas lethargy is recognized to a higher extent with sepsis as compared to NEC (even though HCPs still associate all of these predictors to both sepsis and NEC).

> *"A child with NEC can be agitated and still and a child with sepsis can be agitated and still. But I think with sepsis they would be still more often"*

This distinction is likely due to the higher association of pain to NEC as compared to sepsis:

> *"It is really hard to differentiate sepsis and NEC from each other. Purely on movement, it is not possible I guess. Because at the start they have the same, both are a sepsis-like disease at the start, so you have sepsis-like signs, maybe with NEC, pain, because they have a stomach infection, so pain is a bit more on the foreground there than in the sepsis."*

One nurse practitioner explains NEC as a disease state accompanied by severe, either acute or prolonged (chronic) pain, in which infants exhibit more gross body movements. Whether this behavior is detected or not, depends on several factors. Firstly, the age, as:

> *"A 25/26 week old might be too weak, but a 28/30 week old is more capable of exhibiting these gross body movements indicating they are in pain".*

Second, the location of the pain is important when assessing whether the painful behavior might relate to NEC. Third, some infants show pain early in the disease course, whereas other infants show it later on in the disease course. Fourth, HCPs try to assess a combination of behaviors to determine the type of pain, as it could have different causes e.g. gas in the stomach or a reaction on the feeding.

HCPs described the behaviors related to pain and NEC similar to the general behavior of pain, highlighting the importance of combining signs such as grimace, squeezing the fists, pressing the legs down, stretching the legs or pushing the stomach forward (arching the back). One nurse explained observations of full-body movements in relation to NEC as cyclical behavior initiated by (diffused) squirming, followed by extension of arms and legs, which will ripple off and they become limp before a new cycle starts again (30 sec to 2 min duration). This behavior serves as a predictor of NEC, and it is important to limit, as this cyclical behavior costs a lot of energy for the infants. Another nurse gave a detailed explanation of NEC behavior:

> *"Very restless, high pulse, they scream and can't really find comfort and get calm. And they stretch out, arms in front of the body, they can have a bit of a stop sign with the arms and hands (finger splay). And if they are tired they can put it over the eyes with the hands out (hand on face), because that is like a premature sign. That they got enough stimuli for example. And then you can also get with NEC that they get cramp movements that they pull themselves up, and then stretch out again. So like a little accordion. The duration of these pulling together cramps is very individual. It can be hours, but it can also happen immediately out of nothing. But it happens in intervals because they find some comfort now and then. You can see the high pulse, but the movement pattern is not constant."*

Interestingly, some of the HCPs who related pain to NEC, did not relate lethargy to NEC, whereas other HCPs associated lethargy to NEC as a cause of the pain, in which:

> *"Infants lay completely still in the bed, being unresponsive to everything because of the pain".*

Nevertheless, the large amount of HCPs associating either lethargy or pain, or both, means that it might still be a relation to NEC.

> *"From my experience, children with NEC are either very still, lying very quiet because it hurts so much, and then we often see a very still child with a high heart rate and high blood pressure. Or you see a child that is for a very short time increasingly agitated, also with high blood pressure and heart rate."*

Another finding from the interviews that was particularly interesting was the focus on (lower) limb movements. HCPs associated this as reflective of the abdominal pain as a predictor of NEC where they are "smashing with their legs and bouncing" or pull their legs up and then stretch them out:

> *"Mostly when it is a stomach cramp, the baby just brings up their legs. They curl up or bring up the legs. Or they push their stomach forward (arching of the back). And then stretch the legs. But you see there is something to do with the stomach. If it is severe it can be a sign of NEC, but babies also have a lot of cramps."*

Static extension of lower limbs was, in fact, associated with either pain or swelling from NEC:

> *"If the belly is swollen, then there is inflammation in the peritoneum inside the belly, then you do not want to move your legs because your legs inside are connected to the peritoneum. If this is swollen, then you will not move that, you will be a little bit static. So the legs will not move, more static, maybe a little movement, but limited.."*

There were, however, some disagreement with whether the lower limbs serve as a valuable predictor. Lastly, some HCPs explained infants' inability to get out of an extension as an additional sign.

5.2 APNEA

Central apneas relate to the absence of thoracic movements (and absence of a respiratory signal), signaling no respiratory effort. HCPs believed the pure, central apneas are easily distinguishable from the signal of the monitors.

> *"Apneic infants you can see in different states, so they can be very comfortable and very deep sleep and very at ease and just stop breathing. Those are the most beautiful apneas to see as a clinician and to learn to the residents because they are lying there completely at rest and then you see the thorax going up and down and then nothing happening."*

Obstructive apneas were associated with movements of the thorax and the limbs, e.g. short, "fighting" movements. One neonatologist believed movement sensors can pick up limb and thorax movements associated with obstructive apneas with motion signals, and combining the information with respiration:

> "*For obstructive apneas, the ballistographic film could pick up the large movements if they are also associated with the large thorax impedance movements. But still, you have no flow across the nose or the mouth. That is most important because the obstructive apneas are those apneas which have a lot of movement of the thorax, but no flow. I think obstructive is also associated with some limb activity. If you are choking, then you will move more. I think short movements. A little bit fighting maybe. I think it that subtle that we do not observe it. But I think the pressure foil is relatively sensitive and could pick it up."*

Other HCPs mentioned similar patterns:

> *"For obstructive apneas, they are sometimes moving because feel threatened. Like a grownup having something in the throat, so choking/spitting out milk. So could be moving arms e.g., but sometimes they cant."*

For very young infants who are too weak to show large movements of limbs, obstructive apneas are often seen in the face e.g. sucking movements. Some HCPs only associated movements with obstructive apneas during severe apneic events e.g. infants having an excessive amounts of slime. Only in these cases, they claim that infants show "fighting movements to breathe".

5.3 CEREBRAL HEMORRHAGES

HCPs firstly associated restlessness with severe cerebral hemorrhages. This was often described as agitation, stressful behavior that persist after comforting measures, inability to remain in fetal posture, inability to fall asleep and that the infants will "move around, show effort to cry, and suck on pacifier". One nurse specified that she often associates restlessness with cerebral hemorrhages as a secondary sign if she has reason to exclude NEC. Some HCPs also associated cerebral hemorrhages with lethargy, in which the infants show interchanging behavior between lethargy and restlessness:

> *"The premature can become very limp and tired. Because they have a blood loss, and they don't have that much volume the really small ones. You also see it on the pulse, and they can become notoriously unrested if they have sudden bleeding. But then we would also have thought about it from other parameters we see"*

Second, some HCPs specified that infants can show both big (large amplitude movements) and abnormal movements in the period leading up to cerebral hemorrhages, or smaller movements (with a small amplitude). For instance, a neonatologist expressed small movements that are either generalized or of arms and legs, with an amplitude of 2-3 cm at most. The differences possibly relate to the energy level of the infants, and that they typically show a cyclic pattern with some periods of rest in between. This was expressed by a neonatologist:

> *"They move all the way out, or close to the body. It depends on what they have the energy for, sometimes its just a bit and sometimes the movements are more continuously. So they can keep on moving. But*

sometimes rest periods in between because they are tired. It is difficult to generalize how long time in between the movement periods and the resting. But not comfortable, relaxing, a child with a hemorrhage does not come to rest at all (so you see face grimace, eyes moving, etc.). Keep moving or trying to change position, etc. If they are really little they cant move from themselves."

Third, convulsions/repetitive (abnormal) movements were mentioned by several HCPs. In fact, some HCPs mentioned that convulsions almost always relate to some (cerebral) health deterioration, as clinical convulsions do not occur for no reason.

"When we observe in preterm babies repetitive movements of an extremity, we always think about, is this convulsion due to a hemorrhage, or hypoxic-ischemic encephalitis, which is a little bit different but it is also brain lesions."

One neonatologist expressed the relation of convulsions to cerebral hemorrhages as:

"If the great hemorrhage is associated with repetitive movements, then you can see the differences with a normal baby. It's difficult to explain, but a baby that is irritated and show movement is different, I think you can observe this is different from a baby that is okay and show a lot of movement. If there is nothing to irritate and the baby is irritated, that is not ok. The interaction also gives you a lot of information, it is not only the amplitude or the frequency I think. But the whole picture."

Others described the movements as cramps, shaky movements, fast, jerky movements where "arms jump out, feet jump out, they are not able to properly collect themselves (moving out of fetal posture)". The convulsions can also be very subtle (yet important predictors) which are difficult to notice. For instance, subtle hand movements are difficult to detect, especially if the infant is covered. Noteworthy, some HCPs expressed convulsions as secondary signs after restlessness, which is a more prominent sign of cerebral hemorrhage.

Fourth, HCPs reported "stiff movements", in the form of extended limbs where a nurse expressed that:

"The head comes back and the body is like a banana, with legs sticking straight out, and arms down on the side that sticks straight out (extended lower extremities). That is never a good sign, it is a severe sign for irritated babies, it can be a baby that is cerebrally irritated. But we don't see that often. If they are stiff in the body, it might be a bit less severe but still bad, then they can be notoriously restless. If they are very severe it could also be restless and show a lot of pain".

Nevertheless, the movements expressed above are more prominent in term infants, as they show more robust expressions, as compared to preterm infants who are typically more lethargic.

5.4 Seizures

During the interviews, HCPs expressed it is more important to detect convulsions and separate those from tremors, instead of immediately detecting the seizure type.

"If it needs treatment and research we call it convulsions, and if it doesn't need anything we call it tremors or something like that."

HCPs described convulsions as repetitive, rhythmic movements (e.g. of arms and legs):

"Convulsions are repetitive, rhythmic movements of arms and legs and a typical frequency. Really rhythmic extension-flexion movements. Amplitude 2-3 cm. Sometimes only arms, or one leg, but mostly generalized involving all limbs. It depends on the bleeding (or location of infection)."

Others described it as a continuous process of shaking, possibly with a "stretch movement" where the infants lift their legs (sitting on air). HCPs express challenges in distinguishing convulsions from tremors based on observation, but that they often try to observe the repetitive nature of the movements. Single events are often ignored, as immature infants often have a (benign) uncontrolled twitch in the body (or in one arm/one leg), or a small "sleep shock" just before falling asleep.

> *"Repetitive movements, e.g. hands to the sides or one side. It depends on e.g. what side of the brain it originates from, and how damaged. I think only the repetitive movements in epilepsy are really always pathological. Always. 98% of the cases."*

In addition, benign tremors as less systemic than the pathological where "infants lay there a bit and startle" or they have "premature shaking" or the "back, head, or everything just jumps up, or only hands and legs", or they "shake a little bit and then it stops. It can be a bit on and off."

Other associations with seizures are restlessness and diffuse squirm/wriggling the torso:

> *"They are showing that they are wriggling, so they are with the thorax (moving thorax side to side, a bit like trying to get loose from something). It's a lot of movement, normally such a baby in a snuggle should lie comfortably. They move too much."*

Lastly, seizures were associated with subtle signs that are more difficult to detect during daily care, e.g. eye movements and lip smack.

5.5 PAIN/DISCOMFORT

Predictors of pain and discomfort are either considered as single entities, but more commonly, as a combination of various predictors. In general, behavior that deviates from expected behavior, such as the absence of "comfortable cues" suggests that infants are experiencing pain or discomfort. Examples of comfortable cues are relaxed/open hands, small hand movements, hand in the face/mouth region or hands together. In addition, HCPs expressed several, more specific cues for detecting pain/discomfort.

First, restlessness/agitation were prominent predictors of pain and discomfort. This was often expressed as continuous movements, where the infants typically have shorter periods of resting time as compared to normal. Some mentioned that infants either move in "sudden bursts" with the whole body or one or more limbs, where the behavior of pain is mostly shown in intervals (note that the HR is high during the resting periods of the intervals when they are in pain). Infants move faster as compared to typical comfortable movements that are variable, slow and controlled. HCPs assess infants' activity levels relative to the age, as stronger infants are expected to move more as compared to the very preterm infants. One nurse described that infants typically move in cycles, and to detect how these cycles change and whether the cycles would occur more frequently/closer together, might be a sign of pain/discomfort that requires intervention:

> *"Preterm babies have a real problem with inhibiting their behavior, so they have this repertoire of behaviors, and they do exactly the same thing, and then they stop. And then it's like they ramp up again and do exactly the same thing and then stop. That's the easiest way to teach infant behavior because you can predict what they are going to do next because they almost always do the same. We look after babies with gut problems, and if they are preterm and they have got motility issues, so digestion is painful for them. They do lots of squirming and then they bear down so you hear them grunt, and then they turn very red. And then they will start to extend their arms and legs, and they will ripple of their time and their color will completely change, and it's like they are going completely limp, and then the cycle starts again 30 seconds to 2 minutes time. So it's a lot of energy expended in this cyclical behavior and we really talk to staff about trying to inhibit that behavior, so what can we do to try and support this baby."*

Second, lethargy was associated with pain. Several HCPs expressed this as a possible secondary sign of restlessness, as the infant most likely showed agitation as a response to the pain for a longer time.

Therefore, they eventually run out of energy as if “they give up”, they are “too exhausted to fight the pain” or that they “have a shutdown response, they had too much going on and are tired”. Lethargy associated with pain mostly relates to chronic pain as compared to acute pain. Infants experiencing acute pain e.g. from heal prick might show the behavior of detracting the foot, whereas chronic pain such as for NEC:

> *“which possibly hurts for days show another aspect of pain, where the effect change over time and they become almost depressed, very flat, etc.”.*

Another possibility of lethargy as an association to pain relates to the possibility of the pain level being so high that the infant is “lying completely stiff on the surface to avoid the pain”. In fact, one neonatologist expressed that the infants get so quiet that distinction of extreme pain and comfort becomes a challenge:

> *“The only thing I found difficult is that more and more of the NIDCAP gods they say that whenever the baby is uncomfortable they go into some sort of freezing state. Right, so people that say if I turn on music very loud or put on my car or vacuum cleaner, my baby likes that because it's going to sleep. And actually, it's freezing up and then it goes from an I’m going to die state, I’m really scared state, to I’m just going to surrender. So it really goes from lying still is also pretending to be dead because I'm going to be eaten state. So it’s a bit difficult to say oh, lying still is the same as being comfortable. Because if any animal in the whole world sees a threat, it plays dead. So just try to look that if you really scare a kid they all play dead. So movement is not the same as, you have to be careful with that, you have to take into account heart rate, (and other predictors to create a multimodal algorithm).”*

Third, in line with the previous argument, lethargy in combination with a tonic extension of extremities might be a sign of extreme pain (or even illness), in which “the movements are constant when the baby is really in pain. So they would lay for example with the arms stretched.” A nurse practitioner expressed:

> *“When you see no movements at all and the baby is in extension, so you see limbs extended in a situation in which the baby does not receive any analgesics or sedatives, then all the alarm bells are ringing for me. In terms of this baby is really sick, or maybe even in extreme pain.”*

Any behavior of extended extremities, either lateral or straight up in front of the body is considered a sign of pain by most HCPs. One nurse explained extension up and up and out with arms and /or legs:

> *“We call it salute, so their arm up, so they almost, it's like their arm goes up and out. But they do the same with the legs (sitting on air), but depending on the baby it might be one arm or one leg. Finger splaying, toe splaying is another sign of stress or distress.”*

Noteworthy, one neonatologist did not associate stretched extremities with pain, as neonatal reflexes often cause infants to move out of the positioning aids.

Fourth, movements with a large amplitude, movements while having the extremities extended (stretch/drown), and movements out of the positioning aids, are considered as signs of pain, or as a response to “stressful situations”. These movements related to discomfort were also referred to as “big movements” (large amplitude), where it “feels like the infants are seeking for something to hold” (grasping), as they also typically grab the finger of the HCP during stressed situations. This was also assumed to be the reason why infants typically “move around with their arms” when they are stressed.

HCPs had different opinions as to whether the extended extremities and infants who are out of a fetal posture as a result of stress, or whether the movements are normal. One the one hand, HCPs associated infants extending their arm(s) (and/or legs) to a certain angle where they are not able to bring the arm(s) back as normal movements, in which:

"They just keep moving uncontrollably because they are not able to get it back and they need help to get it back. And that is all they need. They get uncomfortable because they are not able to control their hands as much as they like."

Other reasons are that the infants are unable to contain themselves without the proper positioning aids, and whenever possible, they will "get free", in which they extend their extremities "because they use the space they have whenever they feel it". One nurse compares this to a "star":

"The baby is being like a star, they lose all their boundaries, and they don't know how to bring themselves back into balance, that is why they move with their hands and their feet. (before we had positioning aids, you saw this constantly happening)."

Another explanation is that HCPs often reposition the infants, and:

"*If infants don't like being in that position they will work very hard to get out of that position. So their legs will be over the side and an arm will be over the side so yea" Or "they might get hot so they will try and get out of their clothing and wrack etc."*

On the other hand, several HCPs associate infants who move out of fetal posture to pain in the behavior repeats. Detecting repetitive extension movements and repetitive movements out of fetal posture assists HCPs in determining the cause of the discomfort or pain. When detected, HCPs provide infants with comforting measures, e.g. repositioning them into the positioning aids, and reassess after 15-30 minutes. If the behavior persists, they often assume it relates to pain. If the behavior relates to discomfort or minor causes, e.g. hunger, a pressure area, etc., the discomfort should disappear quickly after comforting measures. One nurse expressed this:

"S*ometimes you hold a baby, and no matter how much you try to comfort them they are not able to get to rest. And that would be a sign that its more than just being uncomfortable because of the lack of containment, that would be a sign of something else is going on."*

One neonatologist explained it as "taking away the source of discomfort or not":

"I think that it's more difficult to calm down the baby if there is something that you haven't taken away, like a disease like sepsis or something. But if the baby is agitated because it needs attention, I don't know if that is a thing, but then its easier to calm them."

In addition to the repetitive nature of the movements, one nurse mentioned that the "normal" stretching of the legs is much slower, in which the stretching behavior of a stressed infant is "more of a quick movement".

Fifth, infants who are uncomfortable or in pain tend to show more torso movements (wriggling), more trembling, finger splay, and grimace/facial movements.

In addition to these cues, the location of the pain is important:

"If they have stomach problems they will pull the legs up. If its pain from an IV in the foot, they will lay completely stiff and stretch the legs out. And that is not normal for a preterm or a term infant. They are supposed to lay a bit crouched. Not necessarily stretching arms too, but could be. Or just one arm. It depends on how much they are able to move because of the equipment."

As expressed in this section, several cues are important for detecting pain. HCPs expressed the importance of combining different parameters:

"Extreme pain would result in gross movements, frequent movements, so movements with a lot of amplitude. Uncontrolled, so not being, we call it containment so self-regulation, this baby is not able to do that, and tachycardia[24]. When I see those things, together with facial expression, so squeezing of the eye, deepening of the nasal furrow, and eyebrow squeeze, then the number one problem I think of is pain."

[24] Tachycardia is a heart rate increasing above normal resting rate.

6 RESULTS – SURVEYS

The questions in the survey asked for confirmation that a certain movement pattern could indicate a certain clinical case. This section first discusses the inclusion criteria for the questions selected for the survey, before presenting the results per movement pattern, in particular infants moving out of fetal posture and extension of extremities. Following this, I probed all the possible movement patterns for three clinical events (namely pain, severe cerebral hemorrhages, and NEC) which will be discussed per clinical event. Following this, more detailed information about activity level, movement patterns and amplitude of movement in relation to different clinical events are described, before I present findings of motion bursts preceding alarms, the ranking of all the use-cases and additional remarks from the participants. Lastly, the final encoding matrix is presented in Table 3. This encoding matrix contains statistics from the survey.

6.1 INCLUSION CRITERIA FOR SURVEY QUESTIONS

The inclusion of questions selected for the survey was based on the findings from the literature and the interview analysis from Table 2. In this table, each cell that was included in the survey is depicted with an asterisk. The first focus of inclusion in the survey was based on all the orange cells in Table 2. These cells were based on clinical events and the related movement patterns that were not mentioned in the literature but considered important in 3 or more interviews, or that was suggested in the literature and mentioned as important in 2 or more interviews. The second inclusion criteria was based on cells that were not necessarily mentioned by more than 2 or 3 participants in the interviews, but included due to convenience in the structure of the survey question. For instance, Q4 tests the typical activity level associated with various clinical events. As discomfort, pain, sepsis, NEC and cerebral hemorrhages were all highlighted as cells to be tested, it was convenient to include seizures in this question, as an additional row to the matrix question. A third inclusion criterion was based on whether the cell was considered important for other reasons. For instance, Q14 asks for the participant's opinion about alarms preceding cardiorespiratory events. This is an interesting question for the implications of this report, however, a question of this nature was also requested by Philips. Fourth, several HCPs associated pain and discomfort with NEC (N=12), and severe cerebral hemorrhages (N=7) during the interviews. Even though pain and discomfort are clinical events, it was included in the survey questions of NEC and cerebral hemorrhages, as the movement patterns related to these clinical events might overlap with movement patterns of other clinical events.

Thirteen cells of relations between movement patterns and clinical events that were supported in the literature were included in the survey to test for the validity of the responses. These were grimace, tongue extension and grasping for pain, out of fetal posture for pain and discomfort, extension of extremities for pain, discomfort, cerebral hemorrhages and seizures, extension of lower extremities for pain, cerebral hemorrhages and seizures, and lethargy for sepsis.

6.2 FETAL POSTURE

The distributions of agreement scores to Q1 about the indications of infants repeatedly moving out of fetal posture for different clinical events are depicted in Figure 4.

Mean agreement score of the statement that infants repeatedly moving out of fetal posture may indicate stress/discomfort (M=4.1, SD=1.1) was higher than a neutral score of 3, a statistically significant mean difference of 1.06, 95%CI [0.76 to 1.37], t(46) = 6.940, p=.001.

Mean agreement score of the statement that infants repeatedly moving out of fetal position may indicate pain (M=3.5, SD=1.0) was higher than a neutral score of 3, a statistically significant mean difference of 0.47, 95%CI [0.18 to 0.76], t(46) = 3.219, p=.002.

Mean agreement score of the statement that infants repeatedly moving out of fetal position may indicate sepsis (M=2.5, SD=1.0) was lower than a neutral score of 3, a statistically significant mean difference of -0.55, 95%CI [-0.84 to -0.27], t(46) = -3.895, p=.001.

Mean agreement score of the statement that infants repeatedly moving out of fetal position may indicate NEC (M=2.4, SD=1.0) was lower than a neutral score of 3, a statistically significant mean difference of -0.60, 95%CI [-0.89 to -0.30], t(46) = -4.115, p=.001.

Mean agreement score of the statement that infants repeatedly moving out of fetal position may indicate (severe) cerebral hemorrhage (M=2.7, SD=1.0) was lower than a neutral score of 3, a statistically significant mean difference of -0.34, 95%CI [-0.63 to -0.05], t(46) = -2.371, p=.022.

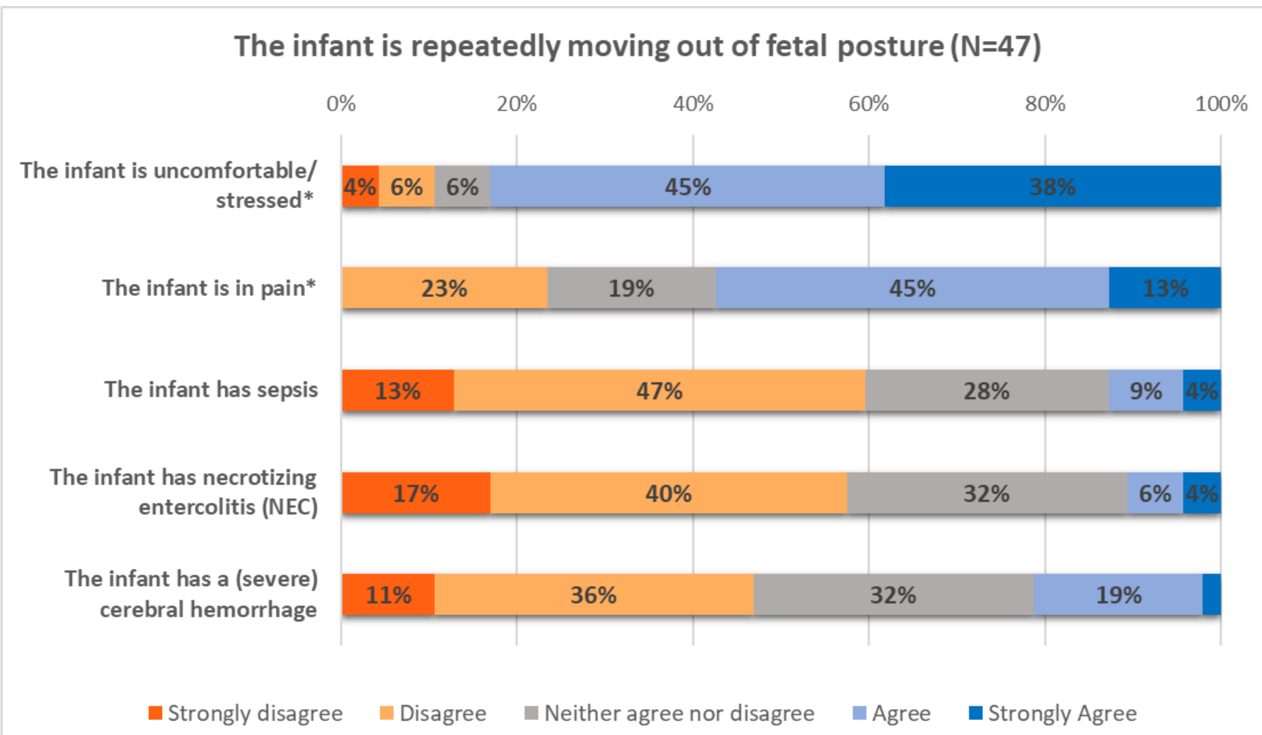

Figure 4: Percentages of agreement rates of infants repeatedly moving out of fetal posture in relation to each clinical event. The significant statements are marked with an asterisk.

6.3 Supine with extended extremities

The distributions of agreement scores to Q2 about the indications of infants lying supine with extended extremities for different clinical events are depicted in Figure 5.

Mean agreement score of the statement that infants in a supine position with extended extremities may indicate stress/discomfort (M=3.9, SD=1.0) was higher than a neutral score of 3, a statistically significant mean difference of 0.94, 95%CI [0.64 to 1.23], t(46) = 6.362, p=.001.

Mean agreement score of the statement that infants in a supine position with extended extremities may indicate pain (M=3.6, SD=1.1) was higher than a neutral score of 3, a statistically significant mean difference of 0.64, 95%CI [0.33 to 0.95], t(46) = 4.162, p=.001.

Mean agreement score of the statement that infants in a supine position with extended extremities may indicate sepsis (M=3.0, SD=1.0) was not statistically different from a neutral score of 3, with a mean difference of 0.04, 95%CI [-0.25 to 0.34], t(46) = 0.292, p=.772.

Mean agreement score of the statement that infants in a supine position with extended extremities may indicate NEC (M=2.9, SD=1.0) was not statistically different from a neutral score of 3, with a mean difference of -0.13, 95%CI [-0.41 to 0.16], t(46) = -0.903, p=.371.

Mean agreement score of the statement that infants in supine position with extended extremities may indicate (severe) cerebral hemorrhage (M=2.9, SD=0.9) was not statistically different from a neutral score of 3, with a mean difference of -0.06, 95%CI [-0.33 to 0.20], t(46) = -0.489, p=.627.

Mean agreement score of the statement that infants in a supine position with extended extremities may indicate seizures (M=2.8, SD=0.9) was not statistically different from a neutral score of 3, with a mean difference of -0.21, 95%CI [-0.49 to 0.06], t(46) = -1.567, p=.124.

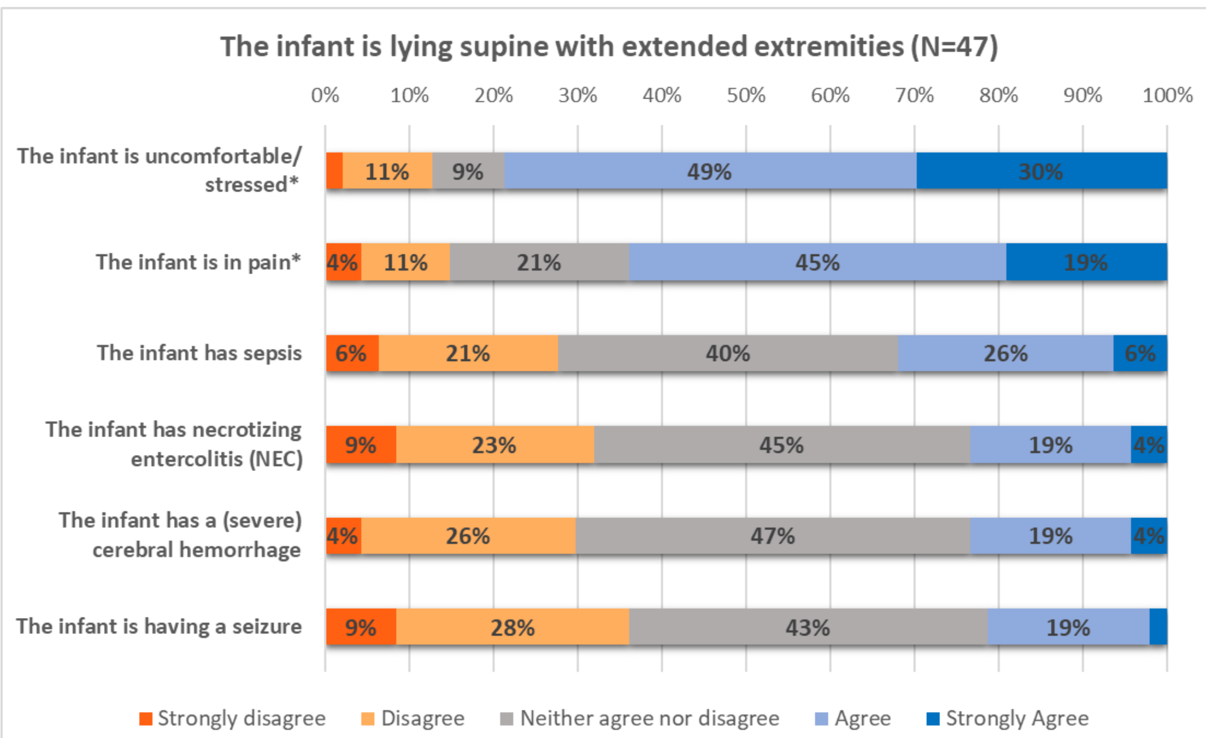

Figure 5: Percentages of agreement rates of infants lying supine with extended extremities in relation to each clinical event. The significant statements are marked with an asterisk.

6.3.1 Repetitive flexion/extension or continuous extension-posture of lower extremities

This subsection presents the results of Q3, which asked whether participants associate repetitive flexion/extension movements or a continuous extension-posture of lower limbs as a possible indicator of health deteriorations. 46 participants answered this question, and they could select multiple answers.

The majority of the participants associated these lower limb movements with pain (61%), with a Wilsons 95% confidence interval of [46%-74%]. The other selected options were seizures (48%) with a Wilsons 95% confidence interval of [34%-62%], severe cerebral hemorrhages (28%) with a Wilsons 95% confidence interval of [17%-43%], and NEC (11%) with a Wilsons 95% confidence interval of [5%-23%]. 15% of the participants selected "other", where they were asked to specify their answer. Two participants mentioned that it occurs if infants are unsupported/need repositioning, whereas others mentioned discomfort, abdominal cramps, and illness. Some participants who selected others expressed that it depends on other parameters as well, such as on gestational age, the condition of the infant, previous movement patterns and non-attenuated care procedures. Nevertheless, two participants mentioned that lower limb activity is a useful area to investigate, given the mentioned parameters are considered. 17% of the responses did not associate the movements with any health deteriorations.

6.4 NEC

33 participants assessed the occurrence of different movement patterns in the case of NEC of Q11. The distributions of occurrence scores are shown in Figure 6.

Only "movement patterns in relation to pain" was indicated to have high occurrence in relation to NEC, with a mean occurrence score (M=3.5, SD=0.9) higher than a "sometimes" score of 3, a statistically significant mean difference of 0.52, 95%CI [0.18 to 0.85], $t(32) = 3.15$, $p=.004$.

Most of the other movement patterns were skewed towards rarely. Tremors (M= 2.6, SD=0.9) had a mean occurrence score lower than 3 with a statistically significant difference of -0.45, 95%CI [-0.79 to -0.12], $t(32) = -2.78$, $p=.009$. Diffuse squirm/wriggle the torso (M=2.6, SD=0.8) had a mean occurrence score lower than 3 with a statistically significant difference of -0.45, 95%CI [-0.74 to -0.17], $t(32) = -3.29$, $p=.002$. Salute (M= 2.4, SD=0.9) had a mean occurrence score lower than 3 with a statistically significant difference of -0.64, 95%CI [-0.95 to -0.32], $t(32) = -4.08$, $p=0.001$.

Fisted hands (M= 2.9, SD=0.9) was insignificantly skewed towards rarely, with a mean occurrence score lower than 3 of -0.15, 95%CI [-0.48 to 0.18], $t(32) = -0.926$, $p=.361$. Fisted hands relate to "sometimes" with polarization is seen with 21.1% selections of rarely, whereas 18.2% selected often.

Flexion/extension movements of lower limbs were insignificantly skewed towards rarely (M=2.82, SD=1.0) with a mean occurrence score lower than 3 of -0.18, 95%CI [-0.52 to 0.16], $t(32) = -1.099$, $p=.280$.

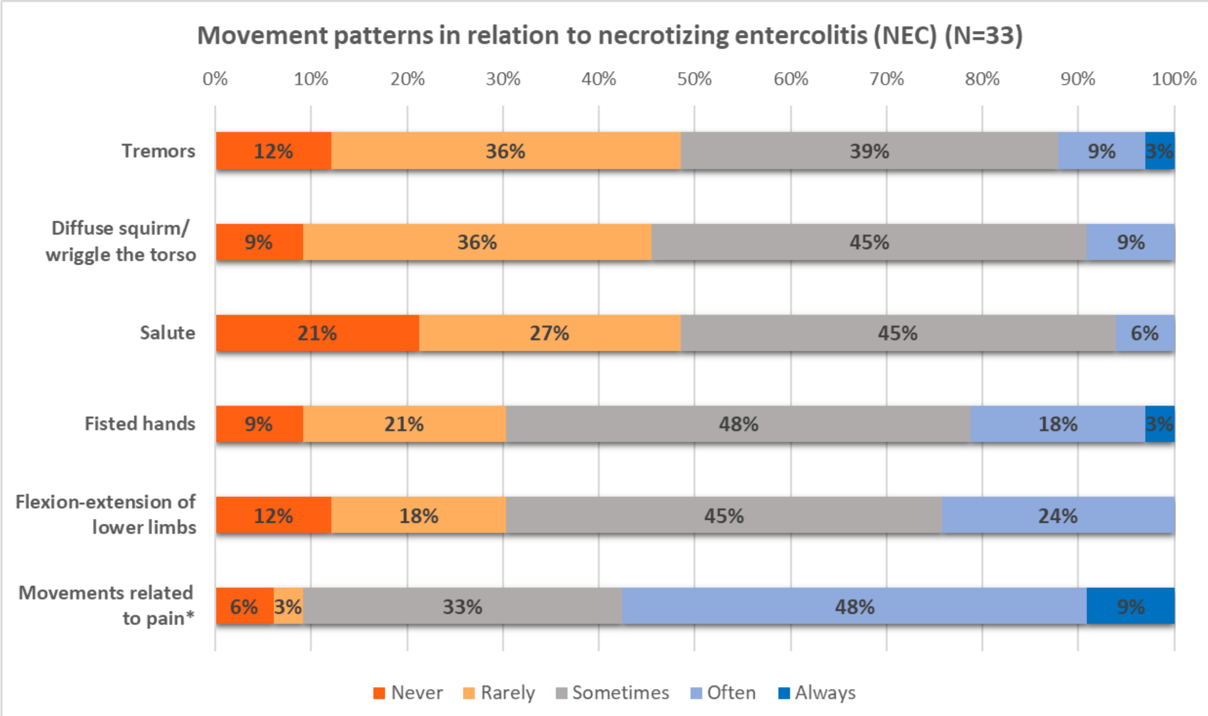

Figure 6: Percentages of responses for the occurrence rate of different movement patterns in relation to NEC. The significant statement is marked with an asterisk.

6.4.1 Sepsis vs. NEC

Q12 assessed whether there characteristic motion patterns that distinguish the onset of sepsis and NEC. 35 participants answered this question, where the majority (77%) answered that the motion characteristics are the same for both clinical events. The participants, who answered that there are distinguishing motion patterns between sepsis and NEC (23%), were asked to specify. 3 participants mentioned that lethargy is (possibly) more associated with sepsis, whereas 5 participants mentioned that pain is more related to NEC. One participant mentioned that "infants with NEC rarely move", where lethargy was mentioned as a predictor of NEC as well:

> *"Different in that sepsis doesn't necessarily cause pain symptoms and pain movements. Babies with sepsis and babies with NEC after often very quiet and can deteriorate rapidly."*

Another participant expressed the difference between term and preterm infants:

> *"Sometimes more characteristics of pain during the onset of NEC and more flaccidity and being more still for preterm infants during the onset of sepsis. For term infants with early sepsis, I see more irritability and movement, but not the facial appearances of pain."*

6.5 Pain

The selected movement patterns in relation to pain for Q6 are shown in Figure 7. 35 participants answered this question, and they were able to select several answers. Only "grimace" and "the infant remains agitated, despite comforting" were significant with all of Wilsons 95% confidence intervals above 50%, as depicted in Figure 7. Grimace in relation to pain added to the survey as a validity check (as it was already clear from the literature), and selected by 97% of the participants. Flexor movements were not chosen by any participant, and the two "other" remarks were finger splay and that "the infant can be very still" (e.g. for severe NEC).

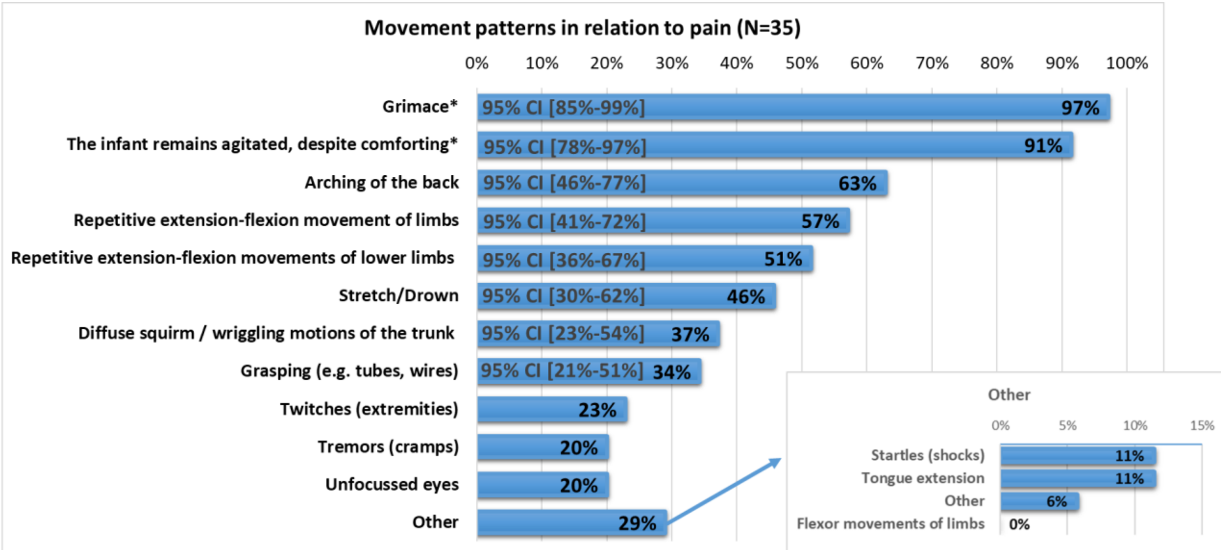

Figure 7: Movements associated with infants experiencing pain. Each bar depicts the percentage of the total number of the 35 participants who selected that answer. The supported statements are marked with an asterisk.

6.5.1 Speed of movement when experiencing pain

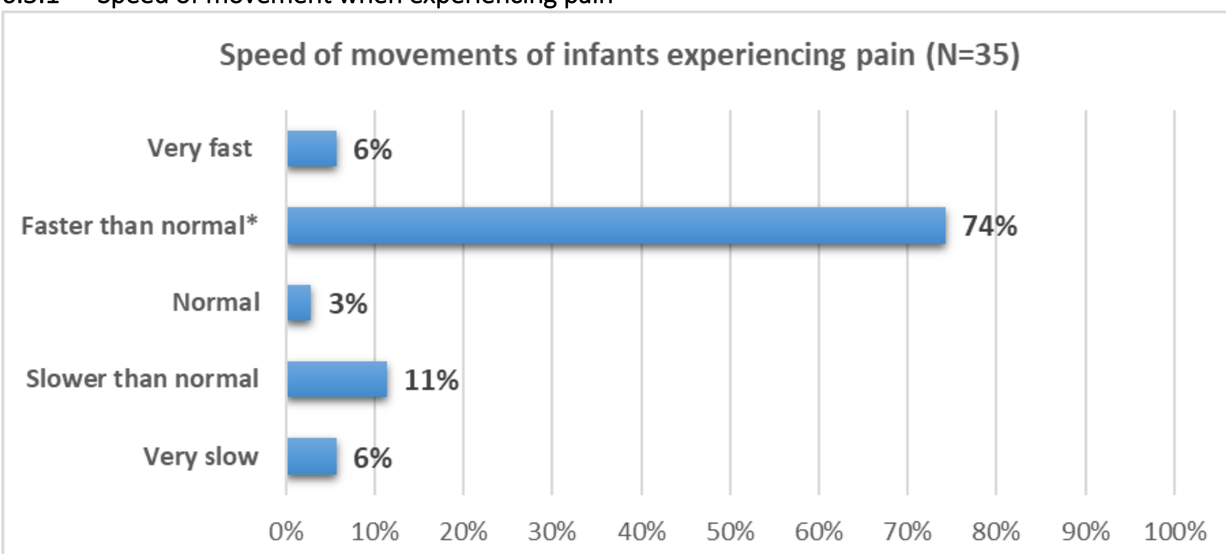

Figure 8: Survey responses on the speed of movement in relation to pain. The supported statement is marked with an asterisk.

Q7 assessed the speed of movements of infants who are experiencing pain (M=4.63, SD=1.0) which had a mean score higher than 4 (normal movement) with a statistically significant difference of 0.63, 95%CI [0.29 to 0.96], $t(34) = 3.82$, $p=.001$. The distribution of responses is shown in Figure 8.

6.5.2 Distinguish discomfort and pain

Q8 asked for the most important distinguishing factors between discomfort and pain. 36 participants answered this question. Several participants mentioned that the distinction depends on (gestational) age, prior pain experience, underlying disease state (associated pathology), behavioral state, environmental factors, use of pain medications and the location of the pain. Also, individual differences were mentioned (that infants have their own pattern), or that the difference is very small/difficult to distinguish. 5 participants said they were unable to answer this, whereas 6 participants mentioned that they are unable to answer this due to the dependencies mentioned above. Nevertheless, the 25 other participants expressed some distinguishing factors or signs of pain.

Mentioned pain cues included grimace (mentioned 9 times), facial/eye movements (4 times), (repetitive) extension of limbs (5 times), specified for lower limbs (1 time), inability to comfort the infant (inconsolability) (5 times), arching of the back (4 times), lethargy (3 times), squirming/movement from side to side (3 times), restlessness (2 times) and fast movements (1 time). One participant mentioned that it really depends on the location of the pain, as arching/guarding is typical for abdominal pain, whereas (acute) pain in other locations is different. Another participant referred to the Neo Comfort scale.

Cues mentioned (each 1 time) for discomfort were (fast, without control) extension/flexion movements of limbs, restlessness, tongue extension, startles, grasping and quick reactions to touch.

Only 6 participants mentioned specific distinction pairs (rather than just saying what they relate to pain), two of them being agitation despite comforting (pain) versus calming ability after comfort (discomfort). The other four pairs were:

> *"Grimace, arching of the back (pain) versus repetitive flexion/extension of limbs, tongue extension, startles, grasping (discomfort)"*
>
> *"Generalized writhing (pain) versus quick responses to touch (discomfort)"*
>
> *"Arching, extension of limbs (pain) versus restlessness, continuously moving (discomfort)".*

The last participant mentioned some distinctions, nevertheless, that it depends on their strength:

> *"In my experience, will (preterm) baby's be very still when they are in pain (if they have the strength to show their pain, it could be with arching, squinting eyes, squirming, grimacing) I think stress is mostly shown with fast and 'without control' movements (extensions – stretching, etc.)"*

These responses indicate that, also for HCPs, the distinction is not very clear, as several of the pain-cues were mentioned as a distress cue, and vice versa.

6.6 Cerebral hemorrhages

The selected movement patterns in relation to (severe) cerebral hemorrhages for Q9 are shown in Figure 9. 35 participants answered this question, and they were able to select several answers. Only "convulsions" was significant with all of Wilsons 95% confidence interval above 50%, as depicted in Figure 7.

Participants who selected abnormal movement patterns and "other" were asked to express this. They mentioned arching position, decorticate/decerebrate movements, plantar flexion of ankles with leg extension, repetitive cycling (2), toe flexion or extension, index finger flexion, persistent thumb adductions, "hands that move away", staring. Furthermore, overall movements such as poor repertoire movements, cramped movements, cramped synchronized movements, chaotic movements, slow and semi-fluent movements, tremors/clonus (2), convulsions, no synchronicity, and that "one side of the body moves differently from the other side". In addition, lethargy / subtle change in behavior was mentioned, however, one participant expressed that they see lethargy in the beginning, but after a while (days), the infants are tenser. Another participant mentioned that the movements depend on how long time after the hemorrhage occurred. (Other responses to abnormal movements were weakened reflexes and no contact). For the comments on "other", participants mentioned lethargy, general movement assessment, agitation and/or alarms of vital parameters and lethargy/seizures.

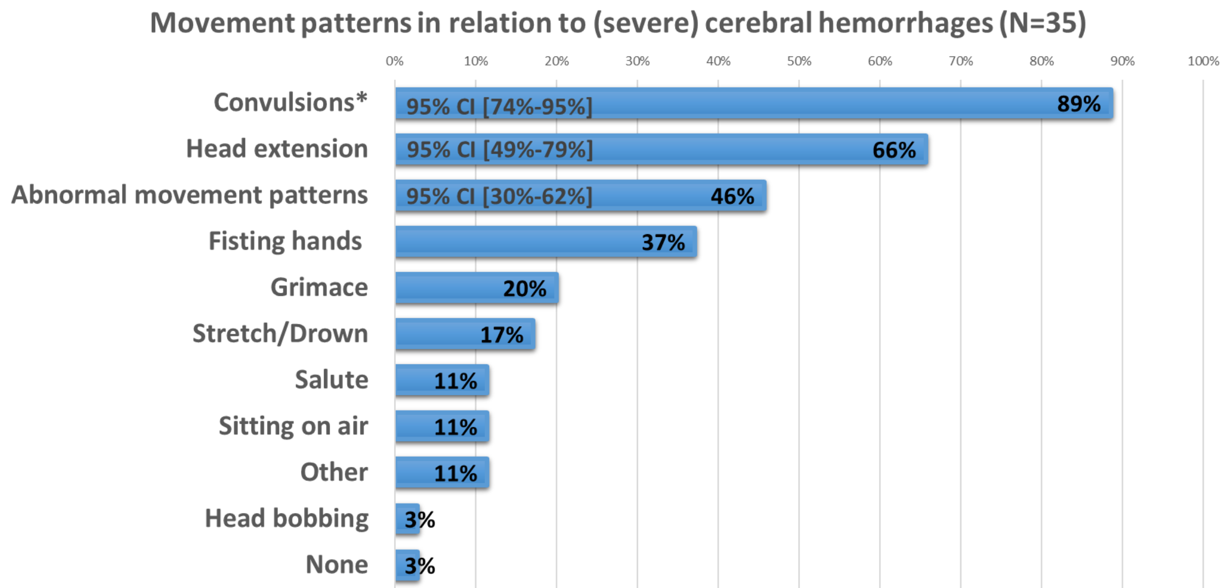

Figure 9: Movement patterns associated with infants having a (severe) cerebral hemorrhage. The supported statement is marked with an asterisk.

6.6.1 Typical behavior associated with cerebral hemorrhages

The distributions of agreement scored to Q10 about the relation of movement patterns to (severe) cerebral hemorrhages are shown in Figure 10.

Mean agreement scores for the relation of (severe) cerebral hemorrhages and convulsions and discomfort/stress were the only two statistically significant related movement patterns. Convulsions (M=3.6, SD=0.9) was higher than a neutral score of 3, a statistically significant difference of 0.60, 95%CI [0.28 to 0.92], t(34) = 3.75, p=.001. Discomfort/stress (M=3.7, SD=0.9) was higher than 3, a statistically significant difference of 0.74, 95%CI [0.43 to 1.06], t(34) = 4.79, p=.001.

Mean agreement scores for behavior related to pain and extension/flexion movements of lower limbs had neutral responses with slight skewness towards agreement, nevertheless, insignificant. Behavior related to pain (M=3.2, SD=0.7) was higher than 3, with a insignificant difference of 0.23, 95%CI [-0.02 to 0.48], t(34) = 1.85, p=.229. Extension/flexion movements of lower limbs (M=3.2, SD=0.9) was higher than 3, with a insignificant difference of 0.20, 95%CI [-0.10 to 0.50], t(34) = 1.36, p=.182.

The statement that infants typically move fast when they have a (severe) cerebral hemorrhage (M=2.8, SD=0.8) was not supported, with insignificant skewness lower than 3 with a mean difference of -0.17, 95%CI [-0.45 to 0.11], t(34) = -1.23, p=.226.

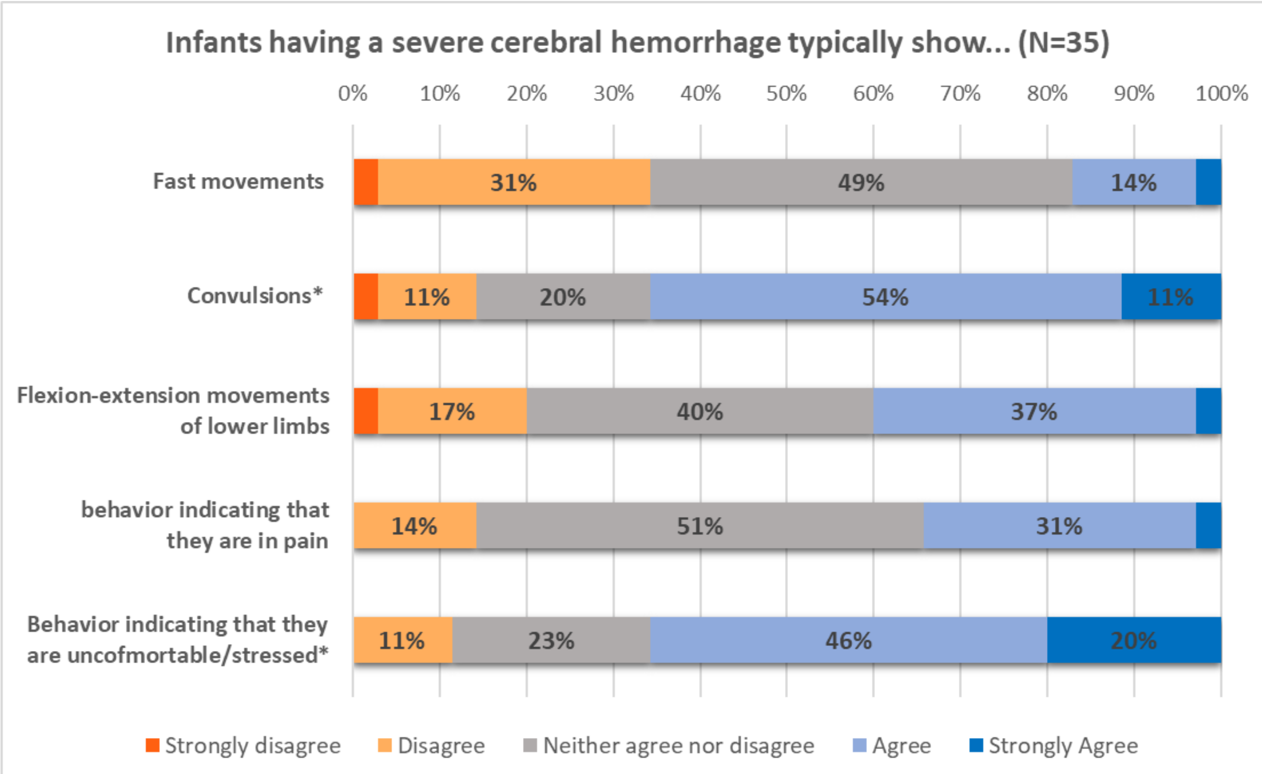

Figure 10: Percentages of agreement rates of movement patterns in relation to (severe) cerebral hemorrhages. Supported statements are marked with an asterisk.

6.7 Activity level

Q4 assessed infants' typical activity level in relation to various clinical events, shown in Figure 11. 43 participants answered this question, and they could provide several answers per clinical event.

The majority of the participants typically associated stress/discomfort with restlessness (Mdn=5), a significant relation with Wilsons 95% confidence interval [62%-87%].

Pain was also associated with restlessness (Mdn=4), a significant relation with Wilsons 95% confidence interval [53%-80%]. Although it was suggested that pain is associated with lethargy, this was not significant with Wilsons 95% confidence interval [22%-50%].

Seizures were associated with restlessness (Mdn=4), an insignificant relation with Wilsons 95% confidence interval [33%-61%]. Combining responses of restlessness and increased activity implies a significant activity level "more than normal" with Wilsons confidence interval [76%-95%]. This does not support the statement of restlessness, rather that infants have a higher activity level as compared to normal.

(severe) cerebral hemorrhages were associated with lethargy (Mdn=2), an insignificant relation with Wilsons confidence interval [33%-61%]. Including the responses of "moving less than normal" is significant with Wilsons 95% confidence interval [73%-93%] suggesting an activity level lower than normal. This does not support the statement of lethargy, rather a suggestion of an activity level lower than normal.

NEC was associated with lethargy (Mdn=2), although insignificant with Wilsons 95% confidence interval [39%-67%].

Sepsis was associated to lethargy (Mdn=2), a significant relation with Wilsons 95% confidence interval [62%-87%].

Although not all associations were significant, this assessment shows the dominating activity level for the clinical events, according to the participants.

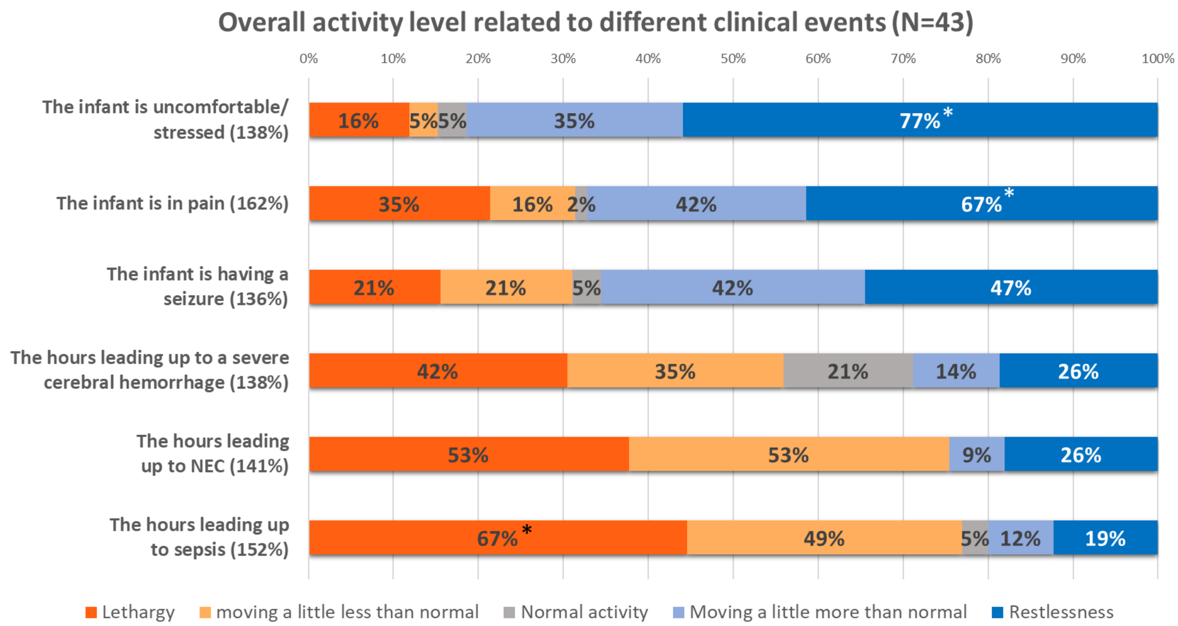

Figure 11: Percentages of participants who selected the different activity levels for the various clinical events. The total percentage for each clinical even is depicted in brackets for each clinical event, and the x-axis depicts the percentage of the total amount of selected responses. Supported statements are marked with an asterisk behind the percentage of the responses.

6.8 Movement patterns

Q5 assessed the different movement patterns in relation to the clinical events pain, seizure, and (obstructive/mixed) apneas. The distribution of responses is shown in Figure 12. 43 participants answered this question, and they were allowed to provide one answer per clinical event.

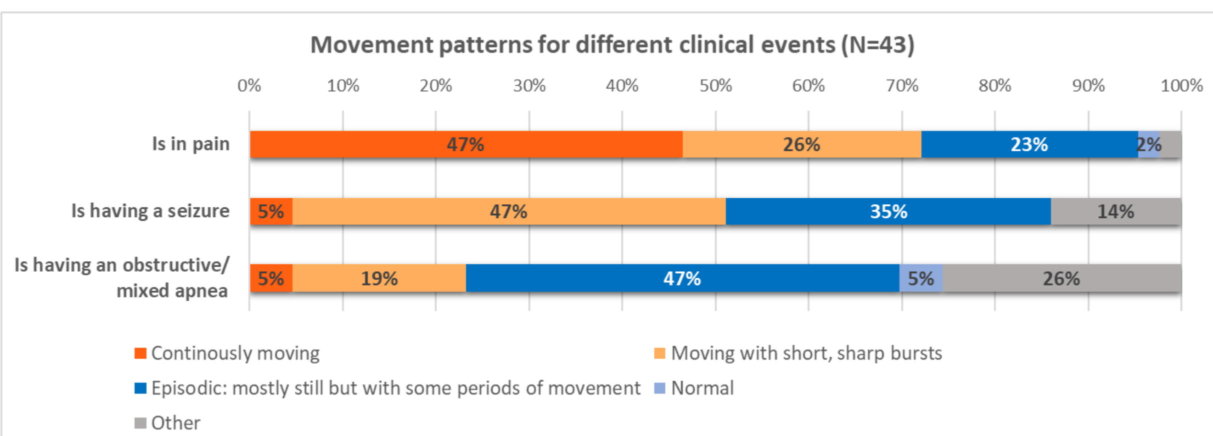

Figure 12: The percentage of responses of the relation between specific movement patterns with different clinical events.

Each of the clinical events had a dominating movement pattern. The majority related pain with continuous movements, seizures with short bursts and obstructive/mixed apneas with episodic movement patterns. All of these relations had a Wilsons 95% confidence interval of [33%-61%], and are not supported.

Even though these were dominating, several participants also related seizures with episodic patterns. Infants in pain could also move with short, sharp bursts (26%) or episodic (23%), whereas infants with obstructive/mixed apneas might show short, sharp bursts (19%). Almost no participants selected normal movement patterns for any of the clinical events, implying that there is a clear difference in behavior during these clinical events. For seizures, the close responses of episodic/bursts might relate to the several different seizure types.

6.9 Amplitude of movement

Q13 assessed the amplitude of movements in relation to different clinical events, where the distributions of responses are shown in Figure 13. 33 respondents answered this question, and the participants could provide one answer per clinical event.

The majority of the participants associated sepsis with movements of small amplitude, a significant relation with a Wilsons 95% confidence interval of [56%-85%]. NEC was also associated with movements of small amplitude, although insignificant with a Wilsons 95% confidence interval of [35%-67%]. Both sepsis and NEC have a descending trend towards movements of large amplitude, as shown in Figure 13.

Opinions seem to be divided with regard to (severe) cerebral hemorrhages, with a polarization of both small amplitude (33%) and large amplitude (27%), both insignificant with Wilsons 95% confidence intervals of [20%-50%] and [15%-44%] respectively.

Infants who are in pain were associated with movements of large amplitude, although insignificant with a Wilsons 95% confidence interval of [38%-70%]. Infants who are uncomfortable/stressed were associated with movements of large amplitude, although insignificant with a Wilsons 95% confidence interval of [35%-67%]. Both “infants who are in pain” and “infants who are uncomfortable/stressed” have a descending trend towards movements with a small amplitude, as shown in Figure 13.

Participants who selected “Other” were not asked to specify their choice.

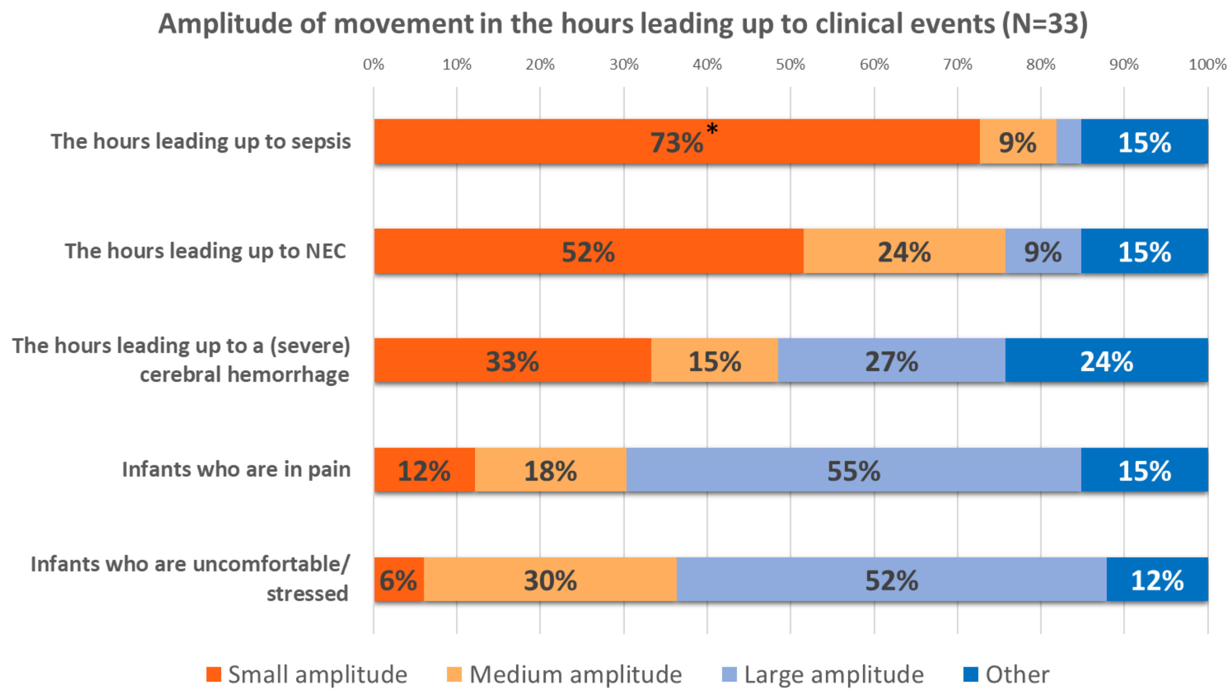

Figure 13: Amplitude of movement selected in form of categories (small, medium, large) in relation to different clinical events. The supported statement is marked with an asterisk behind the associating percentage.

6.10 Alarms

For Q14, participants were asked whether they had noticed infants showing motion bursts (intermittent episodes of movement) preceding a cardiorespiratory alarm in the NICU. 33 Participants answered this question, and participants could select several answers. The responses are shown in Figure 14.

The majority have noticed motion bursts preceding cardiorespiratory alarms in the NICU (more answers were possible). As seen in Figure 14, the most common reason was that motion precedes health deteriorations, nevertheless, several participants mentioned motion artefacts as the reason. As participants could select more answers, there is a possibility that both hold true.

Participants selecting "other" expressed some additional thoughts. Firstly, reflex motions (arching of the back, grimacing) is often seen right before an apnea alarm (when observed), as infants often attempt to support their breathing through a stretch/drown after an apnea. Another participant mentioned the occurrence of motion-bursts preceding alarms for obstructive apneas (or mixed apneas starting with obstruction). In addition, two participants mentioned the delay of the monitor alarms, in which (for instance SpO2) alarm often lag behind events due to averaging, hence, the motion would often precede the alarm/cause an alarm.

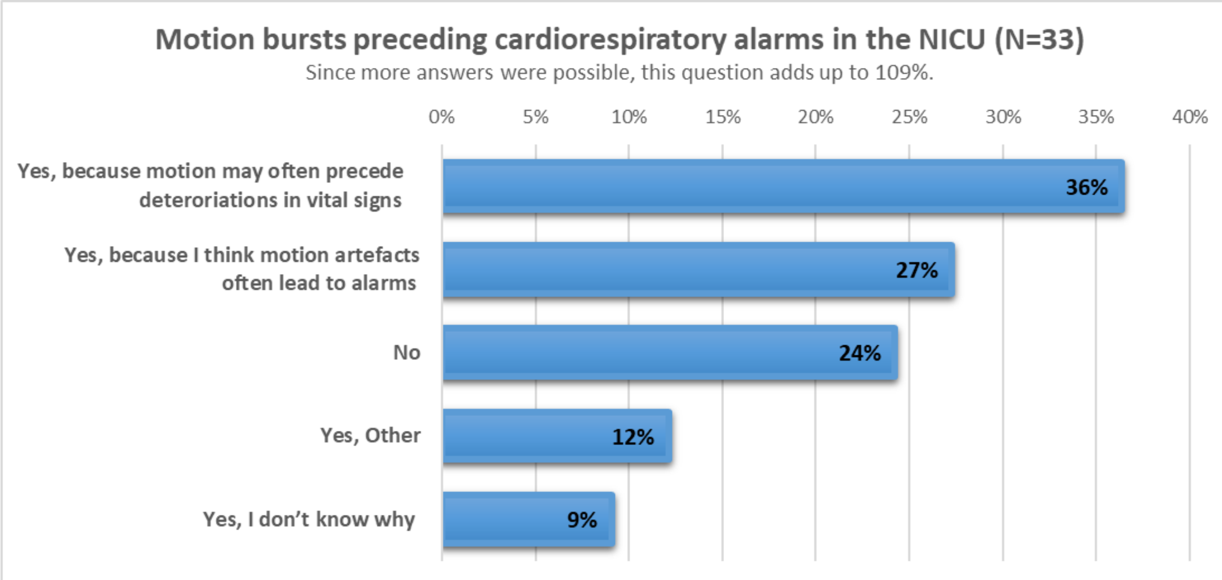

Figure 14: Distribution of answers about motion preceding alarms in the NICU. The 33 participants were able to select more answers, in which the total answers for this question added up to 109%.

6.11 Use-cases

Q15 asked participants to rank each clinical event based on importance. 33 participants answered this question. Participants could select one rank per clinical event.

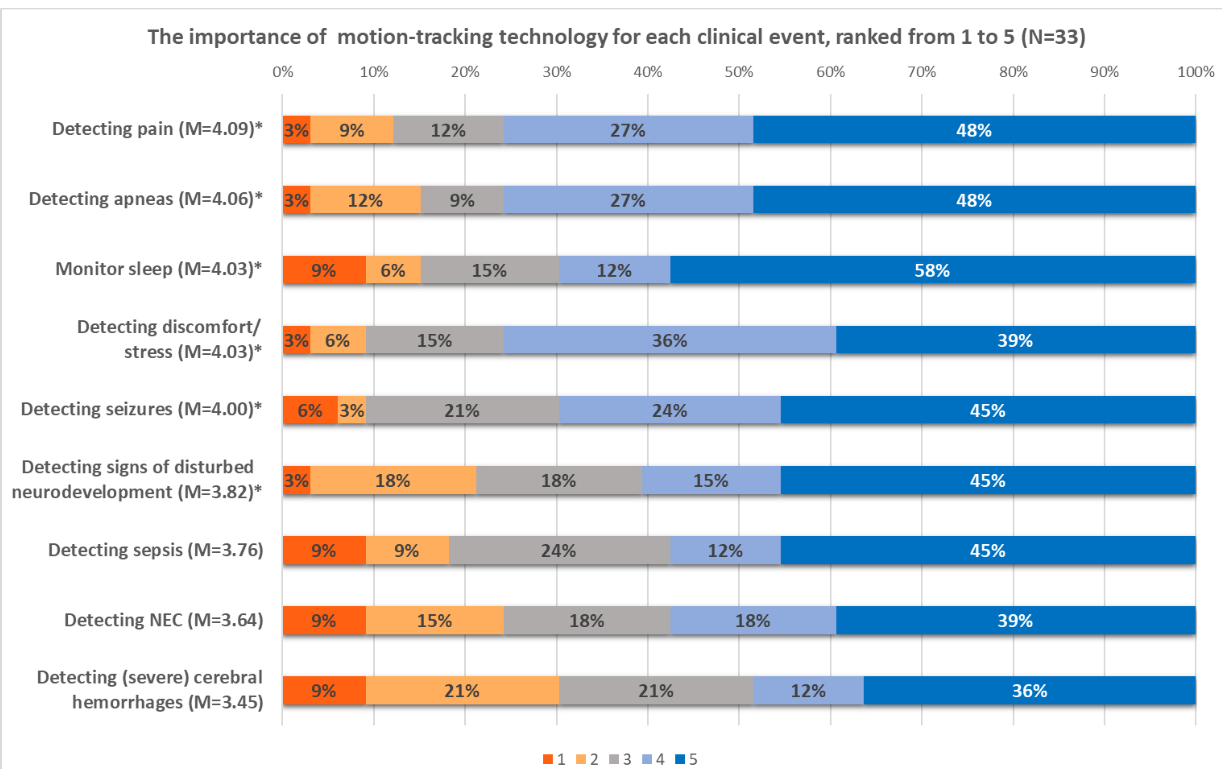

Figure 15: The total number of participants selecting each rank for each clinical event. Each clinical event is ranked from 1 (low rank) to 5 (high rank) based on the importance. The clinical events are sorted by the highest rank mean (from the top) of all the

clinical events asked for to the lowest rank mean (bottom) of all the clinical events. The mean is depicted in brackets after each description, and an asterisk is presented behind the label of clinical events that had a significant rank higher than 3.

Overall, all use-cases were important, as depicted in Figure 15. The most important use-cases that were statistically significantly different from a rank of 3 were detection of pain (p=.03), detection of apneas (p=.01), monitoring of sleep (p=.04), detection of discomfort (p=.04), detection of seizures (p=.04) and tracking neurodevelopment (p=.01). Detection of sepsis, NEC and severe cerebral hemorrhages were insignificantly different from a rank of 3. As seen in Figure 15, sleep monitoring received most of the highest rank of 5.

6.12 ADDITIONAL COMMENTS FROM PARTICIPANTS

For the option of providing additional comments in Q16, participants had several different ideas/opinions about motion tracking technology. Firstly, differentiation in gestational age (and term vs preterm) is necessary as movement patterns and self-regulatory competencies are different. Second, one participant mentioned some issues due to the many individual differences, in particular the environment/effect of care procedures e.g. stress, pain, lack of sleep, etc., and their normal (typical) behavior.

Third, some participants mentioned the value of motion-monitoring to bring additional information (to clinical observations and other tests) for quicker diagnosis. One participant mentioned it could assist in early detection of any deterioration, whereas others specifically mentioned health deteriorations such as sepsis and NEC, or pain monitoring.

Fourth, a participant was positive in this technology in showing/teaching that the general idea of infants being asleep when HCPs are not in the room is not correct, as NIDCAP specialists have reported that struggle and increased movements may go unnoticed in the NICU.

Fifth, one participant mentioned it would be difficult to see/correlate any diseases or stress/pain based on movements, especially because an infant in pain may also be lethargic. Nevertheless, this participant believes it would be useful to track neurological development.

Sixth, also here a participant mentioned the value of the combination of parameters.

> *"I think automated motion detection is valuable when integrated with several other data sources such as heart rate variability, maybe NIRS/aEEG, and algorithms that detect the 'vital signs' alarms that really matter (as opposed to the situation today, where breathing patterns, oxygen saturation, and heart rate are analyzed as separate entities, which, from a physiological point of view, seems weird..."*

Other participants were less positive about the value of motion-tracking technology. Firstly, as it is too unspecific due to the immature sensory and motor systems, and that changes in motion could have several different etiologies. Therefore, the "total picture" and individual differences are important. Even though one participant mentioned it could be useful to monitor wellbeing, he/she believes HCPs "eyes and perception, observation and time to get to know the infants is much more valuable". Second, three participants were skeptical to the implementation of motion-tracking technology in the NICU, as they fear it would replace careful clinical observations, as "monitors are a tool to help and should not become a way of assessing pain". Another participant mentioned an additional issue of parent satisfaction and trust:

> *"Motion-sensing monitoring would be taking away the skill and expertise of the bedside NICU nurse. There is no 'one size fits all' when it comes to recognizing patient deterioration. I also wonder what a parent would think if they're relying on the monitor to recognize signs of deterioration in their baby rather than the nursing and medical teams."*

6.13 ENCODING MATRIX

The encoding matrix is depicted in Table 3. The meaning of the colors are depicted in the label.

Table 3: Encoding matrix after surveys. The statistics from the survey are added to each cell. Cells from the Likert scales contain descriptive statistics, whereas cells from other questions contain the percentage of participants who selected the responses. Supported cells that were calculated with Wilsons 95% confidence intervals contain the confidence intervals, in addition to the percentage of the selected responses. Light shaded blue cells were already supported from the literature. Medium shaded blue cells were supported in the literature and in the survey. Dark shaded blue cells are supported in literature and were also supported in the survey.

Supported in the literature | Supported in the literature and in the survey | Newly supported from the survey

Clinical event / Posture	Discomfort / stress	Pain	Sepsis	NEC	Cerebral Hemorrhage	Seizure	Apnea
(Repeatedly move) out of fetal position	t(46) = 6.940, p=.001	t(46) = 3.219, p=.002	t(46) = - 3.895, p=.001	t(46) = - 4.115, p=.001.	t(46) = -2.371, p=.022.		
Overall activity level (gross body movement)							
Increase / active	77%, Wilsons CI [62%-87%]	67%, Wilsons CI [53%-80%]	19%, Mdn 2	26%, Mdn 2	26%, Mdn 2	47%, Mdn 4	
Lethargy	16%, Mdn 5	35%, Mdn 4	67%, Wilsons CI [62%-87%]	54%, Mdn 2	42%, Mdn 2	20%, Mdn 4	
Movement patterns							
Abnormal movement pattern (different movements from normal)					46%		
"Dynamics" of movement							
Continuously moving		47%				4%	4%
Sharp (short) bursts		26%				47%	19%
Episodic: mostly still but some periods of movements (of approx. 10-20 s)		23%				35%	47%
Cramps/tremor/tremulousness		20%		t(32) = - 2.78, p=.009			
Convulsions					t(34) = 3.75, p=.001 and Wilsons CI [74%-95%]		
Startles (shock, repeating)		11%					
Twitches		23%					
Head/Neck							
Head extension					66%		
Bobbing (up and down) / moving downward					3%		
Face							
Grimace		97%, Wilsons CI [85%-99%]			20%		
Repetitive face movements							
Tongue extension		**11%**					
Specific eye movements		20%					

Torso/trunk							
Diffuse squirm /wriggling the torso		37%		t(32) = -3.29, p=.002.			
Absence thoracic movement (up/down)							
Arching of the back		63%					
Limbs							
Absence of periodic breathing movement							
Extension of limbs (supine)	**t(46) = 6.362, p=.001**	**t(46) = 4.162, p=.001**	t(46) = 0.292, p=.772.	t(46) = -0.903, p=.371.	**t(46) = -0.489, p=.627.**	**t(46) = -1.567, p=.124.**	
Repetitive extension/flexion movement		57%					
Stretch/drown		46%			17%		
Flexor movements		0					
Speed of movement							
Slow		M=4.63 t(34) = 3.82, p=.001.					
Fast		**M=4.63 t(34) = 3.82, p=.001.**			t(34) = -1.23, p=.226		
Low frequency of movements (<6Hz)							
Movement amplitude							
Small range	12%	6%	**73%, Wilsons CI [56%-85%]**	52%	33%		
Large range (move all around)	52%	55%	3%	9%	27%		
Hand/foot clasp							
Upper limbs							
Salute – an extension of arms into midair in front of infant/ Vertical movement in space				t(32) = -4.08, p=0.001.	11%		
Airplane – extends arms laterally							
Grasping /Pulling/grabbing (e.g. tubes/wires)		**34%**					
Hands							
Hand on face / Hand to mouth							
Fisting				t(32) = -0.926, p=.361	37%		
Finger splay							
Lower limbs							
Extension of lower limbs (specifically)		**61%**		11%, Wilsons CI [5%-23%]	**28%**	**48%**	
Repetitive flexion-extension movements of lower extremities		51% and 61%		t(32) = -1.099, p=.280. and 11%,	t(34) = 1.36, p=.182. and 28%	48%	

Sitting on air: full extension of legs into the air					11%		
Correlations with other clinical events as tested in the survey							
Movements related to pain				**t(32) = 3.15, p=.004.**	t(34) = 1.85, p=.229		
Movements related to discomfort					**t(34) = 4.79, p=.001**		

7 DISCUSSION

This research investigated the physiological aspects of infant movements in relation to different clinical events (health deteriorations). By thoroughly analyzing literature in the field, multiple clinical events were recognized, with some relations of movement patterns. Semi-structured interviews provided additional detail to these movement patterns in relation to the clinical events. A survey was conducted to test the validity of these movement patterns, clinical events, and use-areas. Findings suggest that several relations between movement patterns and clinical events exist. As seen in the encoding matrix in Table 3, there are some possibilities for a motion signature per clinical event. Even though this research discovered new relations, some of the relations suggested in the literature and from the interviews were not supported in the survey. This might be caused by the small sample size of respondents in the survey, the limited knowledge about movement patterns in relation to clinical events patterns (again due to short observation, and difficulties detecting subtle signs), or because the associations were single or misinterpreted events when observed by HCPs (during the interviews) and do not exist.

7.1 SURVEY RESULTS

7.1.1 Validity check

Only six of the thirteen cells of relations between movement patterns and clinical events that were supported in the literature and added to the survey as a validity check were significant in the survey. These were moving out of fetal posture and extension of limbs for pain and discomfort, lethargy for sepsis, and grimace for pain.

Tongue extension and grasping were insignificantly correlated to pain (Q6) selected by 11% and 34% of the participants respectively. This is possibly due to the subtle nature of the movements, in which findings in literature often based on longer periods of observation. A second possible explanation of tongue extension being insignificant to pain in the survey is the lack of clarity in the literature of whether it relates to pain or to stress, as expressed by L.Holsti et al. (2005).

Extension of extremities (Q2) were insignificantly correlated with cerebral hemorrhages and seizures. Inspection of Figure 5 even suggests slight skewness towards disagreement. A possible reason for this being suggested in the literature and not in the survey is the translation of specific posturing for tonic seizures (decerebrate or decorticate) that also relate to cerebral hemorrhages, which was not clearly expressed in the survey. As seizures often relate to cerebral hemorrhages, this might explain why the relation was not significant in the survey for either of the clinical events.

Lower limb movements in relation to clinical events (Q3) were expected to relate to seizures, for instance due to the recognized predictor of “stereotypical cycling movements”. This was also expected for cerebral hemorrhages, due to the close resemblance of the predictors of both clinical events. In the survey, however, lower limb movements were insignificant for seizures and cerebral hemorrhages, where 28% and 48% of the participants selected the relations respectively (Q3). Furthermore, “sitting on air” which also resembles lower limb movement was insignificantly related to cerebral hemorrhages in Q9. For flexion/extension movements of lower limbs in Q10, there was slight skewness towards agreement (37%) as compared to disagreement (17%), though also insignificant. Nevertheless, the participants who indicated a relation of lower limb movements to cerebral hemorrhages in the survey and during the interviews, suggest that it is worth investigating this in future studies.

Extension of lower limbs for pain in Q3 was likely insignificant in the survey due to the small sample size, as 61% of the participants selected the possible relation. This resulted in a Wilsons 95% confidence interval of [46%-74%], and as the Wilsons confidence interval was almost above 50%, this might change with larger sample size. Future studies are needed, or a repetition of this survey with more participants.

7.1.2 Fetal posture and extended extremities in relation to clinical events

Literature and interviews suggested repetitively moving out of the fetal posture as an indicator of pain and discomfort/stress, supported in the survey (Q1). During the interviews, repeatedly moving out of the fetal posture was also associated with sepsis, NEC, and cerebral hemorrhages, though insignificant in the survey (Q1). The insignificant findings of the survey and the low number of participants who suggested the relation during the interviews (2 for sepsis and cerebral hemorrhages, 3 for NEC) implied that "repeatedly moving out of fetal posture" is not considered an obvious predictor of sepsis, NEC or cerebral hemorrhages in this research.

Similar to the findings of Q1, an extension of extremities in a supine position in Q2 significantly correlated to pain and discomfort, but not to sepsis, NEC, severe cerebral hemorrhages or seizures. For sepsis, a polarization of opinion is shown for extension of extremities in Q2, where an almost equal number of participants agreed (26%) and disagreed (21%) with the statement. Slight skewness is shown towards agreement, possibly insignificant due to the high number of neutral responses (40% of the participants). The insignificant findings might relate to the lack of clarity of the "stiff limbs" definition as suggested by van den Bruel et al. (2010). During the interviews, HCPs had different explanations of what they exactly meant with stiff limbs, as some referred to high muscle tone, whereas others referred to extension of extremities. In addition, HCPs did not express a "supine position" during the interviews. A more clear definition is needed to test the relation of extended extremities and sepsis in future studies.

7.1.3 Movement patterns in relation to NEC

The only significant relation seen in Q11 in relation to NEC was movement patterns related to pain. This would imply that movement patterns significantly correlated to pain in Q1 and Q2 would also correlate to NEC, however, no such significant correlation was detected. In fact, "out of fetal posture" in Q1 and "lying supine with extended extremities" in Q2 were slightly skewed towards disagreement for NEC. Accounting for 11% of the participants who associated lower limb movements to NEC in Q3, and the participants who mentioned this relation in the interviews, these findings were unexpected.

Possible reasons for these findings are firstly that "lying supine with extended extremities" which relates to pain in Q2 have been missed for NEC due to the "general" classification of extended extremities as mentioned above. Second, it is possible that participants only relate movements of the lower limbs to NEC. During the interviews, some HCPs had quite strong opinions of the extension/pulling up/stamping of lower extremities as NEC predictors due to abdominal pain of the disease, whereas others did not specify any lower limb movement to NEC. In Q3, a proportion of participants related "repetitive extension/flexion or continuous extension-posture of lower extremities" to pain (61%), and to NEC (11%). Inspection of the distribution of responses in Figure 6 for the relation between NEC and flexion/extension movements of lower limbs (Q11), show potential for high occurrence (selected by 24% of the participants), however, due to polarization with the two smaller proportions selecting "rarely" and "never", the sum of these groups suggests skewness towards rarely. This division of opinion possibly relates to the difficulties of detecting lower limb movements in infants, as the infants are mostly covered. Therefore, it might be that lower limb movements relates to NEC, however, it is such a subtle sign that it is not commonly recognized. Accounting for the small proportion of participants who suggested the relation in Q3 and Q11, combined with the statements from the interviewees suggesting that lower limb movement/stiffening of lower limbs are predictors of NEC, there is value in further investigating this relation in future studies. For this, a larger sample size and more focus on the detailed lower limb movements as compared to this study is recommended. If this relation would exist, motion-tracking technology could monitor upper and lower limbs separately to locate the pain towards the abdomen, and hence, increase the likelihood of NEC diagnosis.

The relation of restlessness with NEC (in addition to lethargy) is another suggestion from the interviews that significantly correlated with pain (67%) in the survey (Q4), but not to NEC (26%). Several other pain-related movements were not associated with NEC in this study. This firstly implies either that the pain-related predictors of NEC differs from regular pain-related predictors, or that this exact relation is unclear for HCPs. Second, many of the pain-related predictors tested in the survey associate closer to acute pain as compared to chronic pain, the latter suggested as a sign of NEC during the interviews. Third, the reduced clarity of these relations might caused by a lack of proper detection methods of NEC as suggested by Fox et al. (2015). His findings suggest that HCPs typically look for more obvious signs e.g. large bowel or lethargy, rather than subtle motion signs, as there is not enough evidence for these relations. Nevertheless, it is valuable to further identify the specific pain predictors that relate to NEC. Future research could therefore focus on differentiating the typical behavior related to acute pain versus pain related to NEC manifestation. Collecting and analyzing data from infants in the period before proven NEC might assist in further validating the presence or absence of these predictors, and further separate signs of NEC from other deteriorations.

A secondary objective could be to compare the collected data from infants with NEC onset to data from infants with septic buildup. This might help in differentiating the clinical signs of sepsis and NEC, which were not clear to HCPs during the interviews or in the survey (except for pain relating more to NEC and lethargy relating more to sepsis). Another interesting aspect for further research is to test whether infants with NEC show cyclic behavior of diffused squirming, followed by limb extensions, then a period of lethargy, before the cycle repeats (30s-2min), as suggested by a nurse during the interviews. The current study failed to relate diffuse squirming to NEC in Q11, nevertheless, if this pattern exists, it would be useful for the prediction algorithm.

7.1.4 Movement patterns in relation to pain

Compared to the findings of Grunau et al. (2000) and Morison et al. (2003), this study did not (significantly) associate pain with tremors, opposed to the findings of Holsti et al. (2005). Several other movement patterns significantly correlated to pain, e.g. fast speed of movement and grimace. Some expected correlations of movement patterns to pain were insignificant in the survey, possibly caused by several of the terms in the survey being deduced from the NIDCAP program e.g. “salute” and “airplane”, which is not thoroughly learned by all HCPs. One unexpected finding unrelated to the NIDCAP terms was the insignificance of lethargy as a relation to pain in Q4 of the survey, as several HCPs associated lethargy to pain during the interviews. This insignificant finding is possibly due to the nature of the question, as HCPs could select multiple answers. Therefore, several HCPs might have selected the behavior they associate the most with pain, in this case, restlessness, even though they might relate lethargy to pain as a secondary sign. It is worthwhile to test whether lethargy could be an additional predictor of pain in future studies, as it would be a valuable addition to a pain detection algorithm.

As evident from the interviews and from the survey (Q8), the distinction of pain and discomfort was not obvious. Figure 11 in Q4 indicates that the number of participants (35%) who related lethargy to pain was almost twice as high as compared to the participants who selected lethargy to discomfort (16%). Lethargy as a distinguishing factor for pain and discomfort was not mentioned in Q8. Even though the relation of lethargy to pain was insignificant in Q4, it implies an increased probability of an infant experiencing pain (and not stress) if the infant shows signs of lethargy in addition to the signs of pain/discomfort. Future research could investigate this.

From a technological perspective, detection of activity level in infants could determine the probability of different clinical events. For instance, detection of decreased activity level is more likely related to sepsis or NEC, and less likely related to seizures, and vice versa for detection of restlessness. Similar findings were detected for the amplitude of movement (Q13), with a clear dominance of small amplitude for sepsis and NEC, and large amplitude for pain and discomfort.

7.1.5 Movement patterns in relation to cerebral hemorrhages

Convulsions significantly correlated with cerebral hemorrhages both in Q9 and in Q10, whereas movement patterns in relation to discomfort significantly correlated to cerebral hemorrhages in Q10. An unexpected finding was the insignificant correlation between restlessness and cerebral hemorrhages in Q4, where 26% of the participants agreed and 14% suggested infants to be “moving a little more than normal”. HCPs clearly associated restlessness with severe cerebral hemorrhages during the interviews, even considered a stronger predictor than convulsions by some. On the other hand, some HCPs expressed that they typically do not expect cerebral hemorrhages in the absence of convulsions, where it might be that the periods of restlessness have been missed/not associated to cerebral hemorrhages by HCPs. Future studies should investigate this. The participants who selected lethargy (42%) and “moving a little less than normal” (35%) to cerebral hemorrhages suggest that most HCPs associate cerebral hemorrhages more with lethargy as compared to restlessness. It might be that lethargy is a secondary sign following restlessness, though further research is necessary.

Only one person associated head bobbing to cerebral hemorrhages in the survey, whereas 66% associated head extension to cerebral hemorrhages (Q9). Even though head bobbing was expected to relate to cerebral hemorrhages from the interviews, these findings are possibly caused by the lack of clarification between preterm and term infants. These findings suggest that movements with the head are associated with cerebral hemorrhages, though a head extension is seen instead of head bobbing, possibly because preterm infants lack the strength to lift their head.

The lack of specification of age characteristics possibly also relate to the divided responses of amplitude of movement (Q13) for cerebral hemorrhages. The majority of the participants (33%) associated cerebral hemorrhages with movements of small amplitude, however, the difference if not too big as compared to the number of participants (24%) who associated cerebral hemorrhages with movements of large amplitude. These nonspecific findings are similar to the findings of the interviews. There is a possibility that term infants show large amplitude of movements, which preterm infants lack the energy for.

The responses for the other clinical events in Q13 and activity level Q4, illustrate that the responses are distributed over all categories for cerebral hemorrhages, as compared to the distribution of responses for the other clinical events. The other clinical events had a more clear dominance of one movement category in relation to the clinical event as compared to the other movement categories. For instance, even though most of the participants selected lethargy and a small amplitude of movement as a relation to cerebral hemorrhages, lethargy and movements of small amplitude were more clearly defined for sepsis.

The lack of significant findings for expected movement patterns (and the large proportion of participants who selected unexpected relations from the literature) indicates a lack of understanding of movement patterns in relation to cerebral hemorrhages. This does not necessarily mean that the tested relations do not exist. The prevalence of cerebral hemorrhages in the NICU is rather small when compared to, for instance, sepsis and NEC. Therefore, HCPs might have more experience with observing infants with these more common deteriorations, and less sensitized to cerebral hemorrhages. In addition, HCPs already expressed that signs of cerebral hemorrhages are nonspecific and difficult to detect unless they are severe, and even then, the signs are not obvious.

7.2 Use-cases for technology implementation

This study presented various movement patterns, activity level and postural changes in relation to the presented clinical events. Technology that detects these movement patterns and is able to relate them to the associating clinical event can translate these relations into meaningful information to improve caregiving in NICUs. HCPs expressed various use-cases for motion-tracking technology, as presented in Appendix D, and ranked them based on importance in Q15 of the survey. Evident for monitoring of all the presented clinical events was the need for a multimodal prediction model that combines various parameters for prediction. A combination of parameters is necessary for accurate predictions, but also to separate different conditions from each other, as most of the predictive movement patterns are related to multiple clinical events. In addition, the presence of a single sign has lower sensitivity of prediction of a clinical event, as compared to the presence of several predictive signs.

This multimodal prediction model should output a long-term visualization of continuous movement patterns and changes in posture/activity level in combination with vital signs. A long-term visualization would assist in increasing HCP's available information about infants' behavioral changes and recognize typical behavioral patterns for each infant to detect deviations from normal behavior, while accounting for individual differences of behavior. Recording the data from this multimodal algorithm enables data collection, where HCPs can inspect the data in hindsight, valuable e.g. to track the maturation process of each infant, as highlighted in section 11.2 and 11.2.3 in appendix B. Therefore, motion-tracking technology can create a standardized and subjective common language of automated observations while enabling individualized care, more visibility of infant movement and the infants' condition, long-term recording of patterns for detection of deviations, and possibilities to inspect data in retrospect. In addition, it reduces the reliance on each HCP having to learn how each infant behaves to detect possible deviations. This section discusses implications the discovered movement patterns in relation to the clinical event sepsis as an example of disease and detection of deteriorations, and the clinical event of pain for more regular monitoring during daily care. These two clinical events contained newly discovered relations from this study. Appendix D presents use-cases for the other clinical events from this study.

7.2.1 Sepsis detection

The challenges of detecting sepsis at an early stage in the NICU include the lack of apparent signs early in the course of disease, as many of them are subtle signs. The sepsis has often deteriorated before evident signs are present on the monitors, or shown during the short periods of nursing care (that are often separated with 2-4 hours). The multimodal prediction algorithm could combine the activity level and movement patterns recognized during this study, and combine them with changes in vital signs. This algorithm could in turn provide HCPs with notifications about possible sepsis development, and visualize infant behavior (movements, activity level) in a long-term overview of e.g. 24 hours. This could possibly reduce detection time as compared to current detection methods. The most prominent signs of sepsis were lethargy, movements with small amplitude (and convulsions for term infants), whereas the extension of limbs and restlessness (preceding lethargy) are possible relations to be investigated for further research (as suggested during the interviews).

Detection of lethargy by measuring long-term, continuous recordings of activity level and cyclic patterns over time is a possibility with motion-tracking technology. Accordingly, algorithms can detect deviations from baseline for each infant. For instance, by detecting clusters and intensity of movement, infants who suddenly show reduced movements over 5-6 hours (or even less) are obvious warning signs, as infants typically don't sleep that long. In addition, detection of the relative change from baseline assists in individualized tracking rather than detecting activity level based on a set threshold for all infants. This is important to account for the differences between infants who are naturally active and infants who are naturally less active. For infants who are naturally less active, technology might be able to detect more subtle changes as compared to what HCPs would. Secondary benefits of detecting lethargy and recording infant movement over a longer time are to assess whether the lethargy might be due to other reasons, e.g. tiredness, extreme pain (although lethargy was not significantly correlated with pain in the current study, the relation was suggested during the interviews). This could be detected by, for instance, analyzing whether the infant showed periods of restlessness and pain preceding lethargy, or whether the lethargy occurred for no reason. Ruling out the association of lethargy to sepsis could possibly reduce unnecessary antibiotic treatment because of the insecurity of the presence of disease.

Measuring the range of infant movement enables the detection of movements with small amplitude, and comparison to the normal amplitude of movement for this infant. For the term infants, an addition to the algorithm could be the detection of convulsions (by detecting the repetitive movements). To ensure this only relates to term infants, age characteristics should be accounted for in the algorithm, to assign convulsions as a possible predictor for term infants and leave this out for the preterm infants.

To further increase sensitivity, the algorithm should account for the presence of one or more of these movement patterns or changes in activity level. These should be combined with the vital signs recognized for sepsis in the literature and interviews e.g. bradycardias and apneas, or the other vital signs depicted in section 12.3 in Appendix C. Also for vital signs, considerations of age characteristics could assign stronger weights to apneas and respiratory distress as predictors of sepsis to term infants as compared to preterm infants. Premature infants are expected to have more respiratory distress compared to full-term infants. Therefore, for preterm infants, signs such as apnea and chest retractions are less predictable for sepsis if it occurs as a single, clinical sign, as compared to a combination of various predictors (Verstraete et al., 2015). Nevertheless, detecting apneas and combining it with other predictors might improve accuracy.

Adding statistics to the prediction algorithm could further increase sensitivity, as there is a higher likelihood for young infants who are connected to various monitoring equipment or have undergone more invasive procedures to develop sepsis as compared to other infants. For instance, an infant who is born after 25 weeks who have been in the NICU for more than a week and is connected to the central line has an increased risk of developing sepsis, as the central line is an important reason for bacteria. These probabilities could be tested and trained by learning algorithms. Adding an overview of previous procedures infants have been exposed to adds value, for instance, if an infant has undergone surgery. In this situation, the algorithm should lower the thresholds for the presence of various signs predictive of disease to alert HCPs of possible sepsis.

Future research could investigate additional parameters for the sepsis detection algorithm. For instance, although not tested in the survey, pain/discomfort was associated with sepsis by some interviewees, and not by others. This possibly relates to the lethargy masking the more obvious pain/discomfort behavior, as infants might experience extreme pain while being too exhausted to signal it. As pain typically correlates with tachycardia[25], the addition of HR in the prediction algorithm is valuable to detect whether the pain is indeed a predictor of sepsis.

7.2.2 Comfort scoring – pain detection

The need for detection and monitoring of pain in the NICU is highlighted by HCPs and in literature, for instance by Chen et al. (2012) and L.Holsti (2004). Currently, comfort scoring is a common procedure in NICUs, typically being a one-off measurement per shift (a measurement with a duration of two minutes) that is compared to the previous measurement, often conducted 8 hours earlier. During this period, infants may have shown indications of pain, being unnoticed by HCPs.

Technology that enables continuous pain detection and comfort scoring assists in accurate and timely informing HCPs about infants' who are experiencing pain. Consequently, HCPs can sooner initiate stress reduction strategies and pain management interventions such as sucrose administration, skin-to-skin contact, or facilitated tucking (De Clifford-Faugère et al., 2017). Measuring and collecting the data of long-term patterns (movement patterns, activity, posture) can firstly detect whether the stressed behavior repeats (and hence might suggest pain), whether the nature of the pain possibly relates to health deteriorations, or whether it was a one-time occurrence. Second, it might assist in recognizing the cause of pain. For instance, whether it is caused by a change in posture, lack of postural support, related to feeding, or if the infant showed this behavior for no apparent reason. Knowing the cause of the pain assists in deciding appropriate intervention. Third, data collection and visualization increases HCPs awareness of the presence of painful cues during the current shift and during the previous shift, while enabling more accurate information transfer between shifts. This would help to prevent the delay of the HCPs receiving care to do additional checks e.g. since they see the infant showed pain cues several times in the previous shift. If this is the case, HCPs should be more cautious and possibly intervene faster, as compared to what they would do without this information. Analyzing the data might even inform HCPs whether there is a need to adapt some of the practices in the specific NICU. Fourth, pattern recognition enables individualization, where learning algorithms can detect typical signs of pain from each infant, enabling HCPs to respond accordingly.

[25] Tachycardia is a heart rate increasing above normal resting rate.

A multimodal algorithm that combines the various recognized movement patterns from this research is an alternative/additional option for scoring assessment tools. A combination of parameters (various movement patterns, activity, posture, vital signs) for pain detection increase sensitivity, as pain is often shown in a cluster of predictors, rather than the presence of one single predictor. For example, finger splay and grimace reveal more than only finger splay alone. Several parameters are recognized in this research.

Technology could firstly detect whether infants are repeatedly moving out of fetal posture, or whether they are extending their extremities. For instance, a pressure foil under the mattress as expressed by Joshi et al. (2019) could detect pressure/motion on areas that suggest infants are not lying in the typical posture.

Second, detecting deviations in the baseline activity level of each infant, in this case, an increase in activity level, could detect restlessness. For instance, infants who usually show bursts of motion e.g. 10 times in 10 minutes who suddenly show bursts of movements e.g. 25 times in 10 minutes could indicate restlessness for this infant. The speed of movements could be detected in a similar way (comparing to baseline), as "fast movements" were associated with pain in this study. Adding vital signs to the prediction algorithm is valuable to distinguish whether infants who show increased activity are experiencing pain, or whether they are "comfortably more active". Active infants who are not experiencing pain would not (typically) show an increase in HR, as compared to infants who are experiencing pain who typically have tachycardia. In addition, the SpO2 curve shows a deviating pattern when infants are restless and experiencing pain. Currently, HCPs are not alerted for SpO2 irregularities if the values are within a fixed threshold. As HCPs are not constantly observing the monitors, the addition of these deviations in the algorithm might assist in detecting restlessness that associates with pain. Secondary objectives of tracking activity level in relation to pain is to investigate whether lethargy relates to pain (which was insignificant in the survey) and whether it is a cause of infants being agitated beforehand. For instance, it could assess the previous behavior of the infant to determine whether the infant showed the agitation/restlessness prior to the detected lethargy. This enables detection of whether the lethargy might be a sign of exhaustion (due to pain), due to extreme pain, or due to other reasons e.g. illness.

Third, technology can detect movement patterns deviating from typical comfortable behavior, as recognized in this study. Grimace, facial movements, and tongue extension are recognized predictors from literature, though not always visible to HCPs during care e.g. because large areas of infants' faces are often covered by the respiration support. A camera that continuously records infants may detect more subtle signs as compared to what HCPs can.

Fourth, combining sensory information can detect the movement patterns of upper and lower limbs as recognized in this study (see Table 3) and distinguish movements in the upper- and lower part of the body (Joshi et al., 2018). Locating the pain is useful, as lower limb (extension/flexion) movements possibly mark signs of abdominal pain.

Other important considerations for pain assessment are firstly the history of previous pain exposure. Preterm infants' behavioral pain expression is influenced by their previous experience in the NICU, in which infants who have experienced a greater number of painful procedures may display more motor stress cues, but diminished facial responses to acute pain (L. Holsti, 2004; Morison et al., 2003). For instance, Holsti et al. (2005) found that infants who had been exposed to less pain showed a larger number of lower extremity flexion and extension movements. Second, gestational age is important as both the magnitude of responses and some type of movements differ between term and preterm infants, as expressed by Morison et al. (2003) and Holsti et al. (2005). Smaller and younger infants typically run out of energy faster than older infants do. The prediction algorithm should therefore vary the threshold of the duration of restlessness depending on the age. For instance, a period of 5 minutes of restlessness might indicate pain in an infant of 24 weeks gestational age, whereas 5 minutes of older infants might not. An infant of 27 weeks (gestational or postmenstrual age) might need to show this behavior for 10-15 minutes to indicate pain. Furthermore, both term and preterm infants respond with motor, facial and physiological changes to pain, with the magnitude of responses decreasing as gestational age decreases. Some movements, however, appear unique in preterm infants due to neurological immaturity (L. Holsti, 2004), such as finger splay or a "shut down" response to painful stimuli (Morison et al., 2003). Preterm infants also showed increased body movements associated with acute pain, which may indicate increased pain sensitivity because of sensitization, followed by the "wind-up[26]" phenomenon (Holsti, 2004). In addition, small face-twitches might be a sign of pain in preterm infants, but not to term infants.

7.3 Important considerations for implementation of motion-tracking technology in the NICU

Participants had divided opinions about the implementation of motion-tracking technology in the NICU, as expressed in Q16 in the survey, and during the interviews. On the one hand, some were positive to technology adding additional information to the NICU. On the other hand, HCPs were skeptical of whether the relations of movement patterns to clinical events are strong enough, and afraid that technology would replace valuable observations. This section firstly explains the most prominent consideration related to the current problem of alarm fatigue in the NICU, followed by some other considerations for movement tracking technology in particular.

7.3.1 Alarm management

Alarm fatigue is a recognized issue in NICUs, in which the excessive amount of alarms is a result of each parameter having separate alarms in the current monitoring methods. For instance, a drop in ECG and a drop in SpO2 causes separate alarms; it is a one-time measure, that is not based on combinations or trends. HCPs believe this is an important reason for a large number of false alarms, as well as the many missed important alarms. Therefore, the alarms should be combined, as an addition to the separate visualizations of each vital parameter. Combining the parameters could reduce the threshold of unnecessary alarms. For instance, if there is only a minor change in SpO2 whereas the other parameters are normal, there is no need for an alarm. On the other hand, if there are small deteriorations of several parameters that would often not introduce an alarm separately, the combination might signal the HCPs about the disturbances. This information is important when implementing motion-tracking technology, as several clinical events with the suggested use-cases in this research involve HCPs being alerted for different health deteriorations/changes in movement patterns/changes in activity level. Even though this might suggest additional alarms, a more accurate multimodal algorithm that combines the current vital signs parameters with motion have the potential to improve sensitivity and enable alarms that are more accurate. This would be an important step towards reducing alarm fatigue.

[26] Pain wind-up is the increase in pain intensity over time when a given stimulus is delivered repeatedly.

Adding the movement parameter not only enables detection of changing behavior, but also allows detection of movement artefacts creating signal noise. For instance, monitors often alert for the absence of HR when infants are moving or the absence of respiration when infants are crying. As seen in Figure 14 about motion bursts in relation to cardiorespiratory alarms in the NICU, the majority of HCPs (36%) believe motion bursts precedes deteriorations in vital signs, whereas 27% believe motion artefacts lead to alarms. Artefact rejection by including movement parameters (and combining it with the other parameters) would result in improved accuracy of alarms, possibly enabling quieter environment compared to the current NICU environment. For instance, accurate algorithms notifying HCPs about the presence of apneic events are important, as they often relate to critical events that require intervention. Motion could serve as an additional parameter to reduce motion artefacts and false alarms in the apnea detection algorithm e.g. a neonatologist expressed that he is less concerned about an apnea alarm (no respiration detection) if he detects infant movement and a stable HR, as it is most likely a movement artefact on the respiration detection. The absence of a pulse while also showing an absence in movements, however, is a more critical sign indicating that the infant might indeed have an apneic episode.

Furthermore, motion monitoring could ease the process of EEG analysis, by automatically recognizing movements artefacts. Possible movement artefacts for the EEG signals are currently observed manually on video recordings. Furthermore, a neonatologist believes artefact rejection could improve accuracy in heart rate variability (HRV) tracking for sepsis detection. One HCP suggested visualizing information in a "histogram function":

> *"We have a Philips monitor where you can get oxygen shown in a histogram. And that is better than another type of curve because you can see more how long of the time it's been the different values. That is important to see, but I don't want so many alarms because we want a silent and calm NICU, and often you can reduce the sound from the alarms. So, if it has to alarm it can be but then silent ones. So notifications are nice, but it shouldn't be so many alarms that you don't take them seriously, so alarm fatigue. There must be relevant alarms. But I really want the information, because I can analyze that information."*

7.3.2 Other considerations for the implementation of motion-tracking technology in the NICU

In addition to considerations of limiting the introduction of additional alarms and implementing technology in a continuous, unobtrusive manner, other parameters are important for the motion-tracking algorithm. Firstly, individual differences and age (gestational and postnatal) should be accounted for. Older infants are typically stronger, hence also able to make more movements, different/more variable movements, and movements with a larger amplitude. For preterm infants, the signs are much more subtle, and there should be a threshold in the system as to what predicts deteriorations e.g. more subtle movements could be a risk factor for preterm infants, but not necessarily for term infants. Second, infants who receive medication e.g. sedation often become lethargic. Third, disease history and severity level of deteriorations should be considered when comparing movement patterns and behavioral responses of healthy infants versus infants who have a history of diseases/deteriorations. For instance, infants with gut problems are likely to show more movement cycles as compared to infants without gut problems, whereas infants with neurological conditions are likely to arch a lot more and be tense in their posture. Fourth, the maturation process should be accounted for, where HCPs suggested the exclusion of the first week from the prediction model, as infants need time to adapt to the transition from the intra-uterine to the extra-uterine environment. Therefore, behavioral patterns in the first week might not be representative of the normal behavior of this infant. Fifth, the motion-tracking technology should present the information/notifications/alerts in a clear, understandable way that fits the NICU workflow. This is important, as there are some risks with the automation of observations, in which technology should not replace meaningful observations. HCPs are heavily reliant on numbers to justify reasons to do and not to do things, where some HCPs expressed their worries of nurses blindly trusting the monitors, as they are "rule-based". Therefore, technology should assist in decision-making, rather than risking full reliance on the new monitors eventually intervening with care. Sixth, some HCPs fear issues with data storage, such as duration and location of data storage, as data storage "is a massive issue in hospitals because it's so big". Further research should investigate appropriate methods for methods and duration of storage of the motion-data.

7.4 LIMITATIONS AND FUTURE WORK

The limitations of this study are first that most participants of the interviews were from one hospital in the Netherlands, which has single rooms. During the few interviews with shared-room NICUs, some practices differed, which might have influenced some of the recognized issues. Second, the small sample size of the survey (33/47) might affect the results, e.g. because some movement patterns were recognized by the majority of the participants, however, not significant due to the sample size. The third limitation is that the use of single Likert item questions rather than combined Likert scale questions reduces the possibility to conduct in-depth statistical analysis. The broad scope of this report, however, made it inconvenient to test each relation with several (similar) questions. Fourth, the use of Likert items has several disadvantages such as distortion and central tendency bias (avoidance of using extreme response categories). Fifth, the interviews and surveys were conducted in English, whereas most respondents were not native speakers. This might have resulted in participants not understanding all the questions. Sixth, some parts of the encoding matrix were translated based on interpretations from the interviews. Interpretation of qualitative information always includes the risk that some comments are misinterpreted.

As this study created an initial overview of potential movement pattern relations and applications, many of these cells need clinical testing and further validation. Future work should further investigate the proven cells in the matrix, in addition to the cells that were not proven nor disproven. Several HCPs suggested the involvement of parents in the research of infant movements, as they typically observe infants for longer periods. Therefore, future studies should involve parents in the research, while also considering how to adapt the information from the motion-tracking technology to be representable for parents, and not only HCPs. Furthermore, future research could investigate the potential of motion-tracking technology in developing countries with problems of hiring staff due to budgetary issues.

Successful implementation of motion-tracking technology enables new areas of data collection, both to validate movement patterns e.g. as several HCPs mentioned to notice differences, but are unable to explain them, and to possibly detect new movement patterns. This possibly increases our knowledge span and enables a whole new area of research. In addition, the data is valuable to assess infants' reactions to care procedures, and possibly assist in better planning for these. For instance, some infants respond better by doing daily activities such as heel prick, ultrasound, and x-ray in one go, whereas other infants need it separated, especially younger infants can't do all 3. Future studies could investigate whether the motion-tracking technology could improve individualized care in the NICU.

8 CONCLUSION

This research investigated the physiological interpretation of various motion patterns exhibited by NICU infants. Several movement patterns in relation to various clinical events occurring in the NICU were recognized. Most of these movement patterns are evident in the literature, whereas five new relations were discovered in this study. Firstly, HCPs associated restlessness with infants who are uncomfortable or experiencing pain. Second, convulsions are typically associated with seizures in the literature, and this research discovered that these repetitive movements of convulsions are also associated with an infant with severe cerebral hemorrhage. Third, HCPs recognized that infants who are experiencing pain show fast movements, as compared to a normal, comfortable state. Fourth, infants who are developing sepsis show movements with a small amplitude. Movement patterns that were present in the literature and confirmed in this study include infants who repeatedly move out of fetal posturing for pain and discomfort, lethargy for sepsis, grimace for pain, and extension of extremities while lying supine for pain and discomfort. Contradictory to the literature, this study did not relate the extension of extremities while lying supine with severe cerebral hemorrhages and seizures. In addition to these movement patterns in relation to clinical events, several other movement patterns were suggested, many of them being important for further research.

The findings of this study suggest that there is clinical value in detecting motion patterns exhibited by NICU infants and relate them to clinical events. The discovered relations are not currently used to its full potential in NICUs. Unobtrusive motion tracking technology that fits the NICU workflow and clearly provides HCPs with information about infant motion without introducing additional alarms have the potential to improve caregiving in NICUs. This technology can assist HCPs in providing nursing care by providing automated observations in means of a standardized and subjective overview that reduce HCP's dependency on manually observing and communicating each deviation while enabling individualized care for each infant. In addition, tracking long-term patterns facilitates methods for early detection of health deteriorations by detecting deviations from normal infant behavior and other clinical events, enabling HCPs to react appropriately. It also enables possibilities to inspect data in hindsight, and track maturation. Achieving this requires a technology running a multimodal predictive algorithm translating that accurately detects changes in activity level and movement patterns of infants. Combining this with several vital signs that are currently monitored as separate entities improves accuracy while having the potential to reduce alarm fatigue.

9 REFERENCES

Adde, L., Helbostad, J. L., Jensenius, A. R., Taraldsen, G., Grunewaldt, K. H., & Støen, R. (2010). Early prediction of cerebral palsy by computer-based video analysis of general movements: A feasibility study: Early Computer-based Prediction of CP. *Developmental Medicine & Child Neurology*, *52*(8), 773–778. https://doi.org/10.1111/j.1469-8749.2010.03629.x

Als, H. (1982). *Toward a synactive theory of development: Promise for the assessment and support of infant individuality*. 15.

Als, H. (2009). Newborn Individualized Developmental Care and Assessment Program (NIDCAP): New frontier for neonatal and perinatal medicine. *Journal of Neonatal-Perinatal Medicine*, *3*, 135–147. https://doi.org/10.3233/NPM-2009-0061

Als, H., Butler, S., Kosta, S., & McAnulty, G. (2005). The Assessment of Preterm Infants' Behavior (APIB): Furthering the understanding and measurement of neurodevelopmental competence in preterm and full-term infants. *Mental Retardation and Developmental Disabilities Research Reviews*, *11*(1), 94–102. https://doi.org/10.1002/mrdd.20053

Ambati, V., Ajmera, S., & Akula, A. (2016). A CLINICAL ANALYSIS OF NEONATAL SEPSIS AT NICU (SNCU), WARANGAL. *Journal of Evidence Based Medicine and Healthcare*, *3*(39), 1941–1945. https://doi.org/10.18410/jebmh/2016/432

Basheer, S. (2015). Neonatal jitters. *Journal of Pediatric Neurology*, *08*(01), 005–006. https://doi.org/10.3233/JPN-2010-0364

Bekhof, J., Reitsma, J. B., Kok, J. H., & Van Straaten, I. H. L. M. (2013). Clinical signs to identify late-onset sepsis in preterm infants. *European Journal of Pediatrics*, *172*(4), 501–508. https://doi.org/10.1007/s00431-012-1910-6

Bertelle, V., Sevestre, A., Laou-Hap, K., Nagahapitiye, M. C., & Sizun, J. (2007). *Sleep in the Neonatal Intensive Care Unit*. 9.

Braithwaite, M. (2008). Nurse Burnout and Stress in the NICU: *Advances in Neonatal Care*, *8*(6), 343–347. https://doi.org/10.1097/01.ANC.0000342767.17606.d1

Brazelton, B. T. (1984). *Neonatal Behavioral Assesment Scale* (2nd ed.). Spastics International Medical Publications.

Broom, M., Kecskes, Z., Kildea, S., & Gardner, A. (2018). Exploring the Impact of a Dual Occupancy Neonatal Intensive Care Unit on Staff Workflow, Activity, and Their Perceptions. *HERD: Health Environments Research & Design Journal*, 193758671877936. https://doi.org/10.1177/1937586718779360

Cabon, S., Porée, F., Simon, A., Rosec, O., Pladys, P., & Carrault, G. (2019). Video and audio processing in paediatrics: A review. *Physiological Measurement*, *40*(2), 02TR02. https://doi.org/10.1088/1361-6579/ab0096

Cabon, S., Porée, F., Simon, A., Ugolin, M., Rosec, O., Carrault, G., & Pladys, P. (2017). Motion Estimation and Characterization in Premature Newborns Using Long Duration Video Recordings. *IRBM*, *38*(4), 207–213. https://doi.org/10.1016/j.irbm.2017.05.003

Castral, T. C., Warnock, F., Leite, A. M., Haas, V. J., & Scochi, C. G. S. (2008). The effects of skin-to-skin contact during acute pain in preterm newborns. *European Journal of Pain*, *12*(4), 464–471. https://doi.org/10.1016/j.ejpain.2007.07.012

Cattani, L., Alinovi, D., Ferrari, G., Raheli, R., Pavlidis, E., Spagnoli, C., & Pisani, F. (2014). A wire-free, non-invasive, low-cost video processing-based approach to neonatal apnoea detection. *2014 IEEE Workshop on Biometric Measurements and Systems for Security and Medical Applications (BIOMS) Proceedings*, 67–73. https://doi.org/10.1109/BIOMS.2014.6951538

Cattani, Luca, Alinovi, D., Ferrari, G., Raheli, R., Pavlidis, E., Spagnoli, C., & Pisani, F. (2017). Monitoring infants by automatic video processing: A unified approach to motion analysis. *Computers in Biology and Medicine*, *80*, 158–165. https://doi.org/10.1016/j.compbiomed.2016.11.010

Chatterjee, R. A. (2011). *Is Jitteriness in Newborn Babies Abnormal?* Child Health Explanation. http://www.childhealth-explanation.com/jitteriness.html

Chen, W., Oetomo, S. B., & Feijs, L. (Eds.). (2012). *Neonatal Monitoring Technologies: Design for Integrated Solutions*. IGI Global. https://doi.org/10.4018/978-1-4666-0975-4

Chiesa, C. (2004). Diagnosis of Neonatal Sepsis: A Clinical and Laboratory Challenge. *Clinical Chemistry*, *50*(2), 279–287. https://doi.org/10.1373/clinchem.2003.025171

Collins, M., & Young, M. (2017). Benign Neonatal Shudders, Shivers, Jitteriness, or Tremors: Early Signs of Vitamin D Deficiency. *Pediatrics*, *140*(2), e20160719. https://doi.org/10.1542/peds.2016-0719

Cone, S. (2010). NICU Design: An Opportunity for Change. *Newborn and Infant Nursing Reviews*, *10*(2), 68–69. https://doi.org/10.1053/j.nainr.2010.03.004

Craciunoiu, O., & Holsti, L. (2017). A Systematic Review of the Predictive Validity of Neurobehavioral Assessments During the Preterm Period. *Physical & Occupational Therapy In Pediatrics*, *37*(3), 292–307. https://doi.org/10.1080/01942638.2016.1185501

D'Alleva, A., Leigheb, F., Rinaldi, C., Di Stanislao, F., Vanhaecht, K., De Ridder, D., Bruyneel, L., Cangelosi, G., & Panella, M. (2019). Achieving quadruple aim goals through clinical networks: A systematic review. *Journal of Healthcare Quality Research*, *34*(1), 29–39. https://doi.org/10.1016/j.jhqr.2018.10.010

De Clifford-Faugère, G., Lavallée, A., & Aita, M. (2017). Olfactive stimulation interventions for managing procedural pain in preterm and full-term neonates: A systematic review protocol. *Systematic Reviews*, *6*(1), 203. https://doi.org/10.1186/s13643-017-0589-1

Elser, H. E., Holditch-Davis, D., & Brandon, D. H. (2011). Cerebral Oxygenation Monitoring: A Strategy to Detect Intraventricular Hemorrhage and Periventricular Leukomalacia. *Newborn and Infant Nursing Reviews*, *11*(3), 153–159. https://doi.org/10.1053/j.nainr.2011.07.007

Facini, C., Spagnoli, C., & Pisani, F. (2016). Epileptic and non-epileptic paroxysmal motor phenomena in newborns. *The Journal of Maternal-Fetal & Neonatal Medicine*, *29*(22), 3652–3659. https://doi.org/10.3109/14767058.2016.1140735

Fairchild, K. D. (2013). Predictive monitoring for early detection of sepsis in neonatal ICU patients: *Current Opinion in Pediatrics*, *25*(2), 172–179. https://doi.org/10.1097/MOP.0b013e32835e8fe6

Fernández-Alvarez, E. (2015). Polymorphic, Benign, Nonepileptic, Paroxysmal, Infantile Movements (Fejerman Condition). *Journal of Pediatric Neurology*, *13*(04), 231–236. https://doi.org/10.1055/s-0035-1563383

Finer, N. N., Higgins, R., Kattwinkel, J., & Martin, R. J. (2006). Summary Proceedings From the Apnea-of-Prematurity Group. *Pediatrics*, *117*(Supplement 1), S47–S51. https://doi.org/10.1542/peds.2005-0620H

Fitzgibbons, S. C., Ching, Y., Yu, D., Carpenter, J., Kenny, M., Weldon, C., Lillehei, C., Valim, C., Horbar, J. D., & Jaksic, T. (2009). Mortality of necrotizing enterocolitis expressed by birth weight categories. *Journal of Pediatric Surgery*, *44*(6), 1072–1076. https://doi.org/10.1016/j.jpedsurg.2009.02.013

Foreman, S. W., Thomas, K. A., & Blackburn, S. T. (2008). Individual and Gender Differences Matter in Preterm Infant State Development. *Journal of Obstetric, Gynecologic & Neonatal Nursing*, *37*(6), 657–665. https://doi.org/10.1111/j.1552-6909.2008.00292.x

Fox, J., Thacker, L., & Hendricks-Muñoz, K. (2015). Early Detection Tool of Intestinal Dysfunction: Impact on Necrotizing Enterocolitis Severity. *American Journal of Perinatology*, *32*(10), 927–932. https://doi.org/10.1055/s-0034-1543984

Gephart, S. M., & Quinn, M. C. (2019). Relationship of Necrotizing Enterocolitis Rates to Adoption of Prevention Practices in US Neonatal Intensive Care Units: *Advances in Neonatal Care*, *19*(4), 321–332. https://doi.org/10.1097/ANC.0000000000000592

Grave, G. D., Nelson, S. A., Walker, W. A., Moss, R. L., Dvorak, B., Hamilton, F. A., Higgins, R., & Raju, T. N. K. (2007). New Therapies and Preventive Approaches for Necrotizing Enterocolitis: Report of a Research Planning Workshop. *Pediatric Research*, *62*(4), 510–514. https://doi.org/10.1203/PDR.0b013e318142580a

Griffin, M. P., Lake, D. E., O'Shea, T. M., & Moorman, J. R. (2007). Heart Rate Characteristics and Clinical Signs in Neonatal Sepsis. *Pediatric Research*, *61*(2), 222–227. https://doi.org/10.1203/01.pdr.0000252438.65759.af

Hadders-Algra, M. (2004). General movements: A window for early identification of children at high risk for developmental disorders. *The Journal of Pediatrics*, *145*(2), S12–S18. https://doi.org/10.1016/j.jpeds.2004.05.017

Healthline. (n.d.). *Necrotizing Enterocolitis*. Healthline. Retrieved August 29, 2019, from https://www.healthline.com/health/necrotizing-enterocolitis

Hill, S., Engle, S., Jorgensen, J., Kralik, A., & Whitman, K. (2005). Effects of Facilitated Tucking During Routine Care of Infants Born Preterm: *Pediatric Physical Therapy*, *17*(2), 158–163. https://doi.org/10.1097/01.PEP.0000163097.38957.EC

Holsti, L. (2004). Specific Newborn Individualized Developmental Care and Assessment Program Movements Are Associated With Acute Pain in Preterm Infants in the Neonatal Intensive Care Unit. *PEDIATRICS*, *114*(1), 65–72. https://doi.org/10.1542/peds.114.1.65

Holsti, Liisa, Grunau, R. E., Oberlander, T. F., Whitfield, M. F., & Weinberg, J. (2005). Body Movements: An Important Additional Factor in Discriminating Pain From Stress in Preterm Infants: *The Clinical Journal of Pain*, *21*(6), 491–498. https://doi.org/10.1097/01.ajp.0000146163.30776.44

Huntsman, R. J., Lowry, N. J., & Sankaran, K. (2008). Nonepileptic motor phenomena in the neonate. *Paediatrics & Child Health*, *13*(8), 680–684. https://doi.org/10.1093/pch/13.8.680

Joshi, R., Bierling, B., Feijs, L., van Pul, C., & Andriessen, P. (2019). Monitoring the respiratory rate of preterm infants using an ultrathin film sensor embedded in the bedding: A comparative feasibility study. *Physiological Measurement*, *40*(4), 045003. https://doi.org/10.1088/1361-6579/ab1595

Joshi, R., Bierling, B. L., Long, X., Weijers, J., Feijs, L., Van Pul, C., & Andriessen, P. (2018). A Ballistographic Approach for Continuous and Non-Obtrusive Monitoring of Movement in Neonates. *IEEE Journal of Translational Engineering in Health and Medicine*, *6*, 1–10. https://doi.org/10.1109/JTEHM.2018.2875703

Joshi, R., Kommers, D., Oosterwijk, L., Feijs, L., Van Pul, C., & Andriessen, P. (2019). Predicting Neonatal Sepsis Using Features of Heart Rate Variability, Respiratory Characteristics and ECG-Derived Estimates of Infant Motion. *IEEE Journal of Biomedical and Health Informatics*, 1–1. https://doi.org/10.1109/JBHI.2019.2927463

Joshi, R., van Pul, C., Atallah, L., Feijs, L., Van Huffel, S., & Andriessen, P. (2016). Pattern discovery in critical alarms originating from neonates under intensive care. *Physiological Measurement*, *37*(4), 564–579. https://doi.org/10.1088/0967-3334/37/4/564

Karayiannis, N. B., Xiong, Y., Frost, J. D., Wise, M. S., Hrachovy, R. A., & Mizrahi, E. M. (2006). Automated Detection of Videotaped Neonatal Seizures Based on Motion Tracking Methods: *Journal of Clinical Neurophysiology*, *23*(6), 521–531. https://doi.org/10.1097/00004691-200612000-00004

Kudawla, M., Dutta, S., & Narang, A. (2007). Validation of a Clinical Score for the Diagnosis of Late Onset Neonatal Septicemia in Babies Weighing 1000-2500 g. *Journal of Tropical Pediatrics*, *54*(1), 66–69. https://doi.org/10.1093/tropej/fmm065

Lai, T. T., & Bearer, C. F. (2008). Iatrogenic Environmental Hazards in the Neonatal Intensive Care Unit. *Clinics in Perinatology*, *35*(1), 163–181. https://doi.org/10.1016/j.clp.2007.11.003

Lee, H., Rusin, C. G., Lake, D. E., Clark, M. T., Guin, L., Smoot, T. J., Paget-Brown, A. O., Vergales, B. D., Kattwinkel, J., Moorman, J. R., & Delos, J. B. (2012). A new algorithm for detecting central apnea in neonates. *Physiological Measurement*, *33*(1), 1–17. https://doi.org/10.1088/0967-3334/33/1/1

Ludington-Hoe, S. M., & Abouelfettoh, A. (2013). Light Reduction Capabilities of Homemade and Commercial Incubator Covers in NICU. *ISRN Nursing*, *2013*, 1–9. https://doi.org/10.1155/2013/502393

Mercolini, F., Scarabel, F., Di Leo, V., Nosadini, M., Toldo, I., & Sartori, S. (2015). Baby Jerking: A Teaching Video-Recorded Case of Febrile Myoclonus. *Movement Disorders Clinical Practice*, *2*(4), 429–431. https://doi.org/10.1002/mdc3.12203

Morison, S. J., Holsti, L., Grunau, R. E., Whitfield, M. F., Oberlander, T. F., Chan, H. W. P., & Williams, L. (2003). Are there developmentally distinct motor indicators of pain in preterm infants? *Early Human Development*, *72*(2), 131–146. https://doi.org/10.1016/S0378-3782(03)00044-6

Nakajima, Y., Einspieler, C., Marschik, P. B., Bos, A. F., & Prechtl, H. F. R. (2006). Does a detailed assessment of poor repertoire general movements help to identify those infants who will develop normally? *Early Human Development*, *82*(1), 53–59. https://doi.org/10.1016/j.earlhumdev.2005.07.010

Neu, J., & Walker, W. A. (2011). Necrotizing Enterocolitis. *New England Journal of Medicine*, *364*(3), 255–264. https://doi.org/10.1056/NEJMra1005408

Newnam, K., & Parrott, J. (2013). The NICU Graduate: Implications for Pediatric Primary Care. *Newborn and Infant Nursing Reviews*, *13*(2), 94–100. https://doi.org/10.1053/j.nainr.2013.03.005

NHS. (2017). *Cerebral palsy, symptoms*. National Health Service. https://www.nhs.uk/conditions/cerebral-palsy/symptoms/

Ohgi, S., Arisawa, K., Takahashi, T., Kusumoto, T., Goto, Y., Akiyama, T., & Saito, H. (2003). Neonatal behavioral assessment scale as a predictor of later developmental disabilities of low birth-weight and/or premature infants. *Brain and Development*, *25*(5), 313–321. https://doi.org/10.1016/S0387-7604(02)00233-4

Okada, S., Ohno, Y., Goyahan, Kato-Nishimura, K., Mohri, I., & Taniike, M. (2008). Examination of non-restrictive and non-invasive sleep evaluation technique for children using difference images. *2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 3483–3487. https://doi.org/10.1109/IEMBS.2008.4649956

Orivoli, S., Facini, C., & Pisani, F. (2015). Paroxysmal nonepileptic motor phenomena in newborn. *Brain and Development*, *37*(9), 833–839. https://doi.org/10.1016/j.braindev.2015.01.002

Peyrovi, H., Alinejad-Naeini, M., Mohagheghi, P., & Mehran, A. (2014). The effect of facilitated tucking position during endotracheal suctioning on physiological responses and coping with stress in premature infants: A randomized controlled crossover study. *The Journal of Maternal-Fetal & Neonatal Medicine*, *27*(15), 1555–1559. https://doi.org/10.3109/14767058.2013.868429

Poblano, A., Marquez, A., & Guadalupe, H. (2006). Apnea in Infants. *Indian Journal of Pediatrics*, *73*(12), 1085–1088.

Poets, C. F. (2010). Apnea of prematurity: What can observational studies tell us about pathophysiology? *Sleep Medicine*, *11*(7), 701–707. https://doi.org/10.1016/j.sleep.2009.11.016

Poryo, M., Boeckh, J. C., Gortner, L., Zemlin, M., Duppré, P., Ebrahimi-Fakhari, D., Wagenpfeil, S., Heckmann, M., Mildenberger, E., Hilgendorff, A., Flemmer, A. W., Frey, G., & Meyer, S. (2018). Ante-, peri- and postnatal factors associated with intraventricular hemorrhage in very premature infants. *Early Human Development*, *116*, 1–8. https://doi.org/10.1016/j.earlhumdev.2017.08.010

Prechtl, H. F. R. (1974). *The behavioral states of the newborn infant (a review)*. 28.

Raths, D. (2009). *Information systems improve hospital emergency departments*.

Rosenberg, R. E., Ahmed, A. N. U., Saha, S. K., Chowdhury, M. A., Ahmed, S., Law, P. A., Black, R. E., Santosham, M., & Darmstadt, G. L. (2010). Nosocomial Sepsis Risk Score for Preterm Infants in Low-resource Settings. *Journal of Tropical Pediatrics*, *56*(2), 82–89. https://doi.org/10.1093/tropej/fmp061

Sankar, M. J., Ramesh, A., Aggarwal, R., Deorari, A. K., & Paul, V. K. (2008). Seizures in the Newborn. *Indian Journal of Pediatrics*, *75*, 149–155.

Sardesai, S. R., Kornacka, M. K., Walas, W., & Ramanathan, R. (2011). *Iatrogenic skin injury in the neonatal intensive care unit*. 8.

Seys, D., Wu, A. W., Gerven, E. V., Vleugels, A., Euwema, M., Panella, M., Scott, S. D., Conway, J., Sermeus, W., & Vanhaecht, K. (2013). Health Care Professionals as Second Victims after Adverse Events: A Systematic Review. *Evaluation & the Health Professions*, *36*(2), 135–162. https://doi.org/10.1177/0163278712458918

Shane, A. L., & Stoll, B. J. (2014). Neonatal sepsis: Progress towards improved outcomes. *Journal of Infection*, *68*, S24–S32. https://doi.org/10.1016/j.jinf.2013.09.011

Sikka, R., Morath, J. M., & Leape, L. (2015). The Quadruple Aim: Care, health, cost and meaning in work. *BMJ Quality & Safety*, *24*(10), 608–610. https://doi.org/10.1136/bmjqs-2015-004160

Singh, S. A., Dutta, S., & Narang, A. (2003). Predictive Clinical Scores for Diagnosis of Late Onset Neonatal Septicemia. *Journal of Tropical Pediatrics*, *49*(4), 235–239. https://doi.org/10.1093/tropej/49.4.235

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research*, *104*, 333–339. https://doi.org/10.1016/j.jbusres.2019.07.039

Stevens, B. J., Gibbins, S., Yamada, J., Dionne, K., Lee, G., Johnston, C., & Taddio, A. (2014). The Premature Infant Pain Profile-Revised (PIPP-R): Initial Validation and Feasibility. *The Clinical Journal of Pain*, *30*(3), 238–243. https://doi.org/10.1097/AJP.0b013e3182906aed

Stone, M. L., Tatum, P. M., Weitkamp, J.-H., Mukherjee, A. B., Attridge, J., McGahren, E. D., Rodgers, B. M., Lake, D. E., Moorman, J. R., & Fairchild, K. D. (2013). Abnormal heart rate characteristics before clinical diagnosis of necrotizing enterocolitis. *Journal of Perinatology*, *33*(11), 847–850. https://doi.org/10.1038/jp.2013.63

Sustersic, B., Sustar, K., & Paro-Panjan, D. (2012). General movements of preterm infants in relation to their motor competence between 5 and 6 years. *European Journal of Paediatric Neurology*, *16*(6), 724–729. https://doi.org/10.1016/j.ejpn.2012.05.008

The Lancet. (2016). The unfinished agenda of preterm births. *The Lancet*, *388*(10058), 2323. https://doi.org/10.1016/S0140-6736(16)32170-5

Van den Bruel, A., Haj-Hassan, T., Thompson, M., Buntinx, F., & Mant, D. (2010). Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: A systematic review. *The Lancet*, *375*(9717), 834–845. https://doi.org/10.1016/S0140-6736(09)62000-6

Verstraete, E. H., Blot, K., Mahieu, L., Vogelaers, D., & Blot, S. (2015). Prediction Models for Neonatal Health Care-Associated Sepsis: A Meta-analysis. *PEDIATRICS*, *135*(4), e1002–e1014. https://doi.org/10.1542/peds.2014-3226

Watson, A. (2010). Understanding Neurodevelopmental Outcomes of Prematurity: Education Priorities for NICU Parents. *Advances in Neonatal Care*, *10*(4), 188–193. https://doi.org/10.1097/ANC.0b013e3181e9414b

Weber, M. W., Carlin, J. B., Gatchalian, S., Lehmann, D., Muhe, L., & Mulholland, E. K. (2003). Predictors of neonatal sepsis in developing countries: *The Pediatric Infectious Disease Journal*, *22*(8), 711–717. https://doi.org/10.1097/01.inf.0000078163.80807.88

Werth, J., Atallah, L., Andriessen, P., Long, X., Zwartkruis-Pelgrim, E., & Aarts, R. M. (2017). Unobtrusive sleep state measurements in preterm infants – A review. *Sleep Medicine Reviews*, *32*, 109–122. https://doi.org/10.1016/j.smrv.2016.03.005

Whitelaw, A., & Lee-Kelland, R. (2017). Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD000216.pub2

WHO. (2019). *Preterm birth*. https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth

Williamson, J. R., Bliss, D. W., Browne, D. W., Indic, P., Bloch-Salisbury, E., & Paydarfar, D. (2013). Individualized apnea prediction in preterm infants using cardio-respiratory and movement signals. *2013 IEEE International Conference on Body Sensor Networks*, 1–6. https://doi.org/10.1109/BSN.2013.6575523

Zahed, M., Berbis, J., Brevaut-Malaty, V., Busuttil, M., Tosello, B., & Gire, C. (2015). Posture and movement in very preterm infants at term age in and outside the nest. *Child's Nervous System*, *31*(12), 2333–2340. https://doi.org/10.1007/s00381-015-2905-1

Zupanc, M. L. (2004). Neonatal seizures. *Pediatric Clinics of North America*, *51*(4), 961–978. https://doi.org/10.1016/j.pcl.2004.03.002

Zuzarte, I., Indic, P., Sternad, D., & Paydarfar, D. (2018). Quantifying Movement in Preterm Infants Using Photoplethysmography. *Annals of Biomedical Engineering*, *47*(2), 646–658. https://doi.org/10.1007/s10439-018-02135-7

Zuzarte, I., Indic, P., Sternad, D., & Paydarfar, D. (2019). Quantifying Movement in Preterm Infants Using Photoplethysmography. *Annals of Biomedical Engineering*, *47*(2), 646–658. https://doi.org/10.1007/s10439-018-02135-7

10 Appendix A: Infant monitoring

10.1 Infant monitoring and the NICU

The heart rate in the NICU is recorded with an electrocardiogram (ECG), which records the electrical activity of the heart, by selectively placed (adhesive) electrodes on the skin of the infant (two on either side of the chest and one on the leg or lower abdomen) (Chen et al., 2012). The heart rate activity is represented by complex waveforms containing information about the functioning of the heart, where changes in heart rate can indicate disturbances in homeostasis of the infant (Chen et al., 2012).

Respiration rate can be measured in several ways. One approach is by measuring resistance changes that occur as the diameter of the chest increases and decreases, by attaching a strain gauge around the chest of the infant (Chen et al., 2012). Most NICUs, however, use thoracic impedance plethysmography by using the same electrodes as for the ECG monitoring (Chen et al., 2012). Electrical impedance is then measured between the electrodes on the thorax, in which the impedance is modulated with each inspiration and expiration (Chen et al., 2012). Respiration monitoring is important in the NICUs, as premature infants are at high risk of apneas (absence of pause in breathing), respiratory lung diseases or other conditions due to the immaturity of the respiratory control mechanisms (Chen et al., 2012).

The fraction of oxygen-saturated hemoglobin relative to the total hemoglobin in the blood (oxygenation saturation) is mostly monitored by pulse oximetry (Chen et al., 2012). Pulse oximeters emit lights at red and infrared wavelengths, in which a photodetector measures the absorption of light by the blood and underlying tissue. In the NICU the transmission method is commonly used, in which the light emitter and photodetector are on opposite sides of the palms or feet of the neonate to measure the transmitted light (Chen et al., 2012). A less common method is the reflection method in which the emitter and photodetector are placed next to each other, measuring reflected light (Chen et al., 2012).

In addition to these common parameters, blood pressure and body temperature are important measures in the NICU. Blood pressure is measured by the systolic (heart contracts) pressure and diastolic (heart relaxed) pressure, e.g. either with a pressure transducer connected to an indwelling arterial catheter or indirectly by oscillometry. Normal blood pressure varies between age, nevertheless, too low blood pressure can associate with infections, blood/fluid loss, and medications. Another indicator of infection and hence a critical measure is body temperature (Chen et al., 2012), which helps determine deteriorations while assisting in determining adequate temperatures for optimal growth and development of neonates (Chen et al., 2012).

Brain electrical activity is measured with an ElectroEncephaloGram (EEG) where electrodes are placed on infants' scalp. EEG monitoring can detect apneas and certain types of seizures (among others). Limitations of EEG is that it is an expensive, time-consuming, short-term method of monitoring that require experienced staff. In addition, it is not always available for all infants in full-time NICUs.

10.2 The quadruple aim

This research has the potential to impact all the factors of the quadruple aim by investigating methods (motion-tracking) to improve the safety of infants while assisting HCPs in providing care. Initially, the triple aim was introduced as a framework centered over the goals of improving the individual experience of care, advancing the health of populations (clinical outcomes, effectiveness), and reducing costs of healthcare (financial aspects, efficiency) (D'Alleva et al., 2019; Sikka et al., 2015). The triple aim was adopted in many organizations in order to guide this transition, however, achieving this effective health care system required an additional component of a productive workforce (Sikka et al., 2015). Hence, the addition of improving the experience of providing care (the fourth aim) transformed the triple aim into the quadruple aim (Sikka et al., 2015), a transition illustrated in Figure 16. By successfully implementing motion-tracking technology in the NICU, HCPs have additional information that can assist them/improve their ability to provide care.

Attempts of this transition to an effective workforce are reflected in the changes in technology and practices since the initiation of neonatology (the subspecialty of pediatrics) in the 1940s (Chen et al., 2012). For example, a recent trend of newly designed NICUs has shifted from shared rooms to single-family rooms for each infant (Cone, 2010). This transition is a result of the belief that the physical environment has a significant impact on HCPs, infants and parents, such as better infection control practices, increased family involvement and assured patient privacy e.g. for breastfeeding and kangaroo care (infant kept skin-to-skin with parent) (Cone, 2010). Nevertheless, there are still several imperfections in the NICU environments, such as emotional distress and burnout for HCPs as discussed by Braithwaite (2008); Joshi et al. (2016) and Seys et al. (2013), which relates to alarm fatigue as discussed by Joshi et al. (2016). The rewards of a successful transition to the quadruple aim are immense, as the healthcare environment has the potential to free up resources from inefficient production practices, with the potential to use the resources to save lives, reduce human suffering, and deliver value (Sikka et al., 2015).

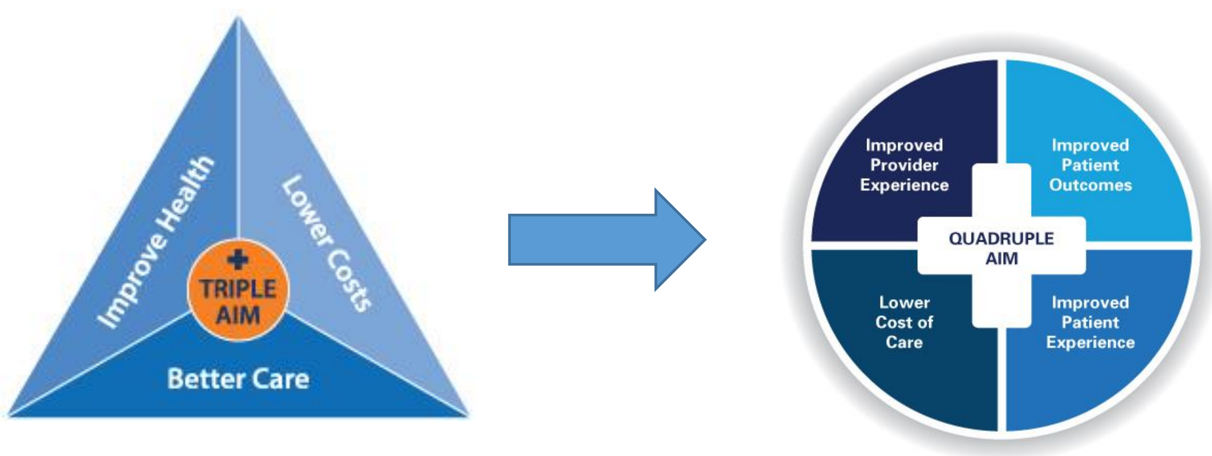

Figure 16: The transition from triple aim to quadruple aim by adding a fourth important component: improving provider experience. Available at (MeHI, n.d.) and (Marquette University, n.d.). Date accessed: 07/05/2019.

10.3 COMFORTNEO

Comfort assessment

Neo Scale

Date/time 1	Date/time 2	Date/time 3	Date/time 4

Sticker with patient's name

Place a mark

		1	2	3	4	
Alertness	1.					quiet sleep (eyes closed, no facial movement)
	2.					active sleep (eyes closed, facial movement)
	3.					quietly awake (eyes open, no facial movement)
	4.					actively awake (eyes open, facial movement)
	5.					awake and hyperalert
Calmness/ Agitation	1.					calm (appears lucid and serene)
	2.					slightly anxious (shows slight anxiety)
	3.					anxious (appears agitated but remains in control)
	4.					very anxious (appears very agitated, just able to control)
	5.					panicky (severe distress with loss of control)
Respiratory response (only in mechanically ventilated children)	1.					no spontaneous respiration
	2.					spontaneous respiration on ventilator
	3.					unrest or resistance to ventilator
	4.					actively breathes against ventilator or coughs regularly
	5.					fights ventilator
Crying (only in spontaneously breathing children)	1.					no crying
	2.					faint crying
	3.					soft crying or moaning
	4.					hard crying
	5.					intense crying or screaming
Body movement	1.					no or minimal movement
	2.					up to three slight arm and / or leg movements
	3.					more than three slight arm and / or leg movements
	4.					up to three vigorous arm and / or leg movements
	5.					more than three vigorous arm and / or leg movements, or whole body
Facial tension	1.					facial muscles fully relaxed, relaxed open mouth
	2.					normal facial tension
	3.					intermittent eye squeeze and brow furrow
	4.					continuous eye squeeze and brow furrow
	5.					facial muscles contorted and grimacing (eye squeeze, brow furrow, open mouth, nasal-labial lines)
(Body) muscle tone (observation only)	1.					muscles fully relaxed (open hands, dribbling, open mouth)
	2.					reduced muscle tone; less resistance than normal
	3.					normal muscle tone
	4.					increased muscle tone (clenched hands and/or clenched, bent toes)
	5.					extreme muscle tone (rigidity and flexion of fingers and/or toes)
Total score						
NRS pain*		...	...	...	...	estimate of pain (0 = no pain to 10 = worst possible pain)
NRS distress*		...	...	...	...	estimate of distress (0 = no distress to 10 = worst possible distress)

Details sedatives/ analgesics ______________________________

Reason assessment ______________________________

(Before or after medication or standard assessment) *Abbreviation: NRS = Numeric Rating Scale

10.4 Seizures table

Table 4: Movement patterns in relation to different types of seizures. The black numbers in the cells depict how many interviews mentioned the relation. The red numbers illustrate the articles supporting the relation from the literature review. The articles can be found in Table 8.

Movement / type of seizure	Tonic seizure	Clonic seizure	Subtle seizure	Myoclonic seizure
Convulsions (repetitive, rhythmic jerks – 1-2 jerks per second, duration at least 10 s)		1, L2, L9, L21, L22		
Twitching of facial, limb or axial muscles		L21		
decorticate/decerebrate posturing. "sustained flexion or extension of axial or appendicular muscle groups"	3,4,6,14,16, L20			
Tonic postures of a single limb or portion of a limb			L9, L20, L21	
Spasmodic jerky contraction of groups of muscles				L19
Head/face				
Moving head downward				L19
Face				
Ocular movements - Sustained eye-opening with unresponsive ocular fixation - Blinking - Cycled fluttering - Eye deviation (horizontal or vertical) Roving eye movements Oral–buccal–lingual movements - chewing, swallowing, sucking, repetitive tongue movements, lip-smacking			L9, L20, L21	
Limbs				
Stereotypic limb movements (bicycling, boxing, pedaling, swimming)			L9, L20, L21	
Extended extremities or extended lower and flexed upper (decerebrate/decorticate posturing) typically lasting 3-10 seconds	L29, L19			
Migrate from one muscle group to others in a non-ordered fashion Frequency: 1-3(4) jerks per second, at least 10 seconds duration (both fast and slow components)		L20, L21, L22		
Single or multiple lighting fast jerks of upper or lower limbs (can occur 15-20 times a day)				L20, L23, L21
Shoulder/limb stiffening				L19
Left hand initially moving slowly, before rapidly moving to the top of the frame.				L23

10.5 INDICATORS OF PAIN

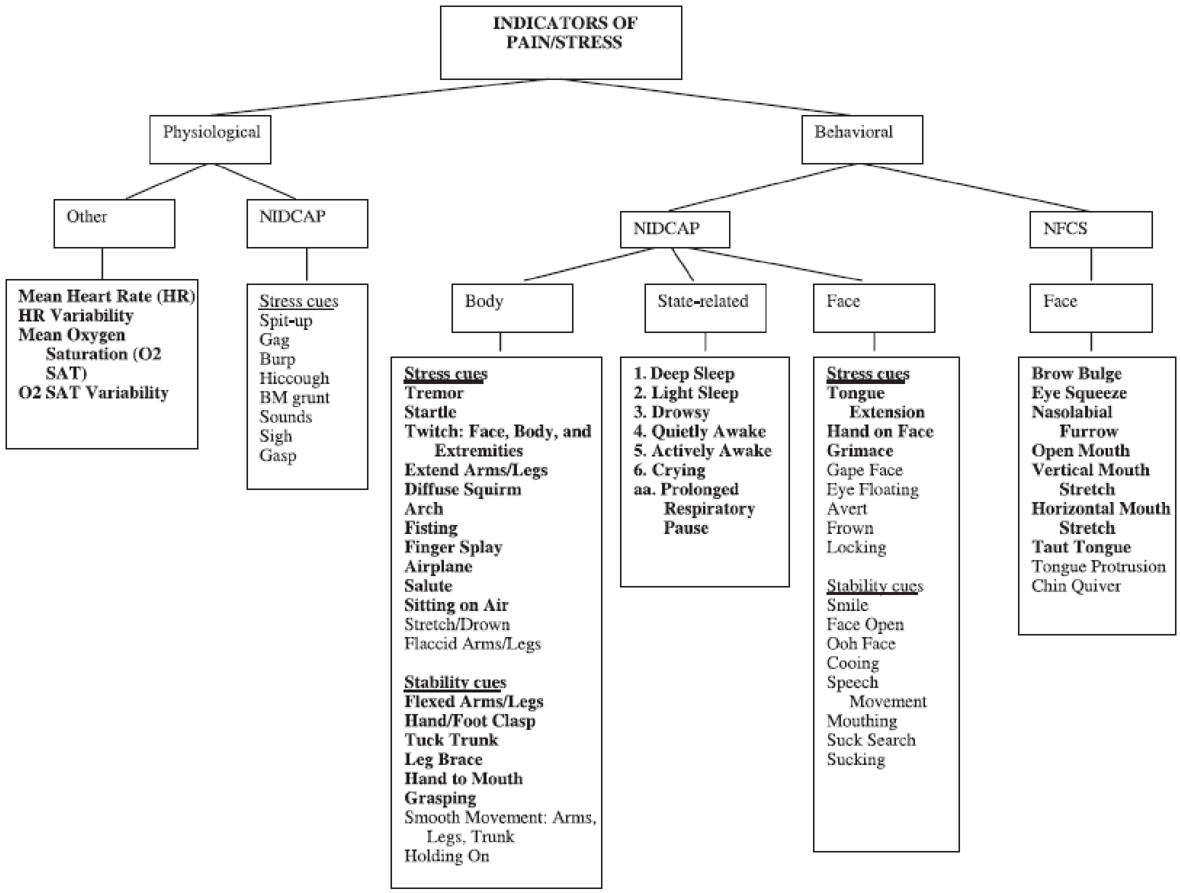

Figure 17: Indicators of pain and stress used in the study by Morison et al. (2003). Indicators in bold were displayed in more than 10% of the observations.

11 APPENDIX B: CLINICAL EVENTS: SLEEP-WAKE AND NEURODEVELOPMENT

11.1 SLEEP-WAKE PATTERNS IN HOSPITALIZED INFANTS

11.1.1 Infant sleep description and impact

Sleep in infants is a predominant behavioral state, and one of the most important factors of neural development (Bertelle et al., 2007; Werth et al., 2017). Development of infant states and state organization is an important task the first week after birth (Als, 1982; Foreman et al., 2008), which is limited in preterm infants due to their immature CNS (Joshi et al., 2018). The limited state organization is often reflected in the difference in quality and quantity of sleep between term and preterm infants, as preterm infants often show unstable development of integrated and coordinated patterns of sleep-wake cycles (Foreman et al., 2008). As opposed to sleep states in adults organized as rapid eye movement (REM) sleep and non-REM sleep, infants younger than 6 months of age are described to have three sleep states, namely active sleep (AS), quiet sleep (QS) and indeterminate sleep (IS) (Bertelle et al., 2007). AS corresponds to REM sleep in adults and is the main sleep state in preterm infants, QS corresponds to non-REM sleep, and IS (or transitional sleep) is when the sleep characteristics are not clearly classifiable as any of the two (Bertelle et al., 2007). The evidence of immature neurologic function in preterm infants is based on periods of AS, often defined by a lack of sleep cycling, shortened sleep periods, shorter periods of QS and undifferentiated sleep states, as compared to full-term infants (Foreman et al., 2008). The dominance of AS over QS puts preterm infants at higher risk for later neurological problems (Foreman et al., 2008), in which state development involves increasing QS, decreasing AS, and smooth and fewer transitions (Als, 1982; Foreman et al., 2008).

Recognition and distinction of sleep states in preterm infants is often a challenge. Studies have failed to detect circadian rhythms in preterm infants, possibly related to the influence of environmental factors (e.g. noise, light) and care activities disrupting the sleep organization (AS/QS ratio, daily sleep duration and increase the number of sleep state transitions), driving the ultradian rhythm (Bertelle et al., 2007). However essential, nursing care activities are serious sleep disrupters, currently planned based on emergencies and patient clinical status, rather than infants' sleep-wake rhythm (Bertelle et al., 2007). As wakefulness in infants is followed by a brief episode of AS, a short episode of IS and eventually QS, infants who are frequently disrupted cannot achieve QS, risking sleep-deprived infants (Bertelle et al., 2007). Short-term sleep deprivation of infants is associated with obstructive apneas and a significant increase in arousal thresholds and pain perception, and it may irreversibly affect brain development (Bertelle et al., 2007). Current methods for identification and evaluation of sleep is with polysomnography (simultaneous recording of EEG, eye movements, breathing rate, and heart rate), or more commonly with behavioral observations (Bertelle et al., 2007; Okada et al., 2008).

Detecting sleep with observation is another challenge, and polysomnography requires facility investment and high personnel cost, in addition to the attachment of electrodes, and stress for the infants (Okada et al., 2008). Another method is videosomnography, in which an analyst visually examines body movements from a recorded video. This method is time-consuming and does not (currently) enable real-time tracking. Other methods include actigraphy, either alone or in combination with other measurements such as heart rate and respiration rate (Werth et al., 2017), or attempts to monitor sleep by measuring body temperature (Okada et al., 2008). Common requirements for sleep-monitoring methods are the need to take precautionary steps to minimize potential harm for environmental hazards for these high-risk infants since preterm infants already have additional light in their environment as opposed to the darkness they are biologically prepared for in the utero. (Chen et al., 2012; Lai & Bearer, 2008; Ludington-Hoe & Abouelfettoh, 2013). Research found that preterm infants' periods of quiet sleep increased sufficiently when being in a dark environment for 2-3 hours longer, compared to a light environment (Ludington-Hoe & Abouelfettoh, 2013). Literature highlights the potential for unobtrusive continuous monitoring methods that also operate in the dark, such as pressure sensors under the mattress detecting heart rate, breathing rate and body movements (Joshi et al., 2018; Okada et al., 2008). Another method is the use of different processing of a video image, as expressed by Okada et al. (2008).

11.1.2 Movement patterns associated with sleep

Several behavioral scales exist to codify sleep states based on clinical observation, with Prechtl's criteria being commonly used (Bertelle et al., 2007). Precthl (1974) describes 5 behavioral states according to the regularity of respiration, open/closed eyes and movements of head and limbs. Descriptions of each state are shown in Table 5 (Bertelle et al., 2007; Prechtl, 1974). In general, states 1-3 (QS, AS, and quiet awake) have an absence of the property of gross body movements, whereas state 4-5 has a presence of the property of the gross body movements. For regulation of respiration, quiet sleep and quiet awake have a presence of these while all the other states have an absence of regularity of respiration.

Prechtl describes respiration as the distinguishing parameter of active and quiet sleep, in which irregular respiration corresponds to AS and regular respiration to QS. In addition, QS contains very little movement, where infants remain in a body posture with small movements such as twitches present sometimes (Prechtl, 1974). During AS, more movement is normal, both gross movement (e.g. limb displacement, writhing movements, stretching) but also more twitches and startles (Prechtl, 1974). Prechtl also mentions that movements occur cyclic, in which they are separated by intervals of a few minutes and lasting for a few minutes.

Table 5: Sleep states described by Prechtl (1974).

State 1	This epoch begins when respiration becomes regular in an infant with eyes closed. It may take some time before the regularity is consistent, especially since sights or apneic spells may occur, nevertheless, respiration rapidly falls back into regularity. Obviously marked irregularities are always transient (lasting shortly) and connected with gross body movements in the form of startles (Prechtl, 1974). The overall breathing rate of 30-40/min and heart rate of 90-110/min jumps to 120-140/min during startles, followed by bradycardia. Writhing movements (twisting) movements are rare in healthy infants a few days old (Prechtl, 1974).
State 2	The most characteristic transitory events are gross movements of one limb or generalized body and head movements, the latter being coordinated either stretches or more commonly irregular writhing movements. The average time of the interval is around 3 minutes, and the gross movements of the baby in this state may lead to changes in the posture of the baby (Prechtl, 1974). In this state, small twitches are common in the face, hands, and feet, but they hardly lead to the displacement of a limb (Prechtl, 1974).
State 3	An average shortest duration of all states, as it is easily shifting to and from states 2 and 4.
State 4	In state 4, eyes are open and movements of arms, legs, and head are normal. How coordinated these movements depend on the position of the infant. For example, in prone (flat, face down) position locomotion and head lift movements may prevail, while in supine (horizontally, face and torso up) position limb movements are less patterned (Prechtl, 1974). During state 4, the activity fluctuates and periods with large gross movements alternate with periods of small movements (Prechtl, 1974).
State 5	Crying

The Neonatal Behavioral Assessment Scale (NBAS) scale defines infant states based on body activity level and face/eye movements (in addition to e.g. regularity of respiration) (Bertelle et al., 2007; Brazelton, 1984; Foreman et al., 2008). Heidelise Als and colleagues adapted the NBAS scale to the NIDCAP program (Als, 2009), based on a regular observation-recommendation cycle around care to promote and respect infant sleep (Bertelle et al., 2007). AS is typically characterized by the presence of REM, irregular respiration, body and facial movement, absence of chin muscle tone (recorded by electromyography (EMG)) and a continuous EEG pattern (Bertelle et al., 2007). QS is marked by the absence of REM and body movements, presence of regular respiration, a tonic chin EMG and discontinuous EEG pattern (varying with gestational age) (Bertelle et al., 2007).

Joshi et al. (2018) analyzed 20 video recordings, in which they identified the presence of specific motion bursts of 20-60 seconds (occasionally up to 2 minutes) occurring every few minutes in all recordings. These motion bursts were large body movements of the head, trunk, and limbs, its repetitive nature suggesting physiological origin (Joshi et al., 2018). In addition, periods of tens of minutes (of 20-hour recordings) with the absence of motion bursts were recognized. Based on findings from Werth et al. (2017), Joshi et al. (2018) suggest that their findings indicate the motion bursts to be reflective of the arousal state of sleep-wake cycles, in which periods without motion bursts potentially correspond to quiet sleep. This reflection was strengthened by the positive correlation between movement bursts and heart rate increase, which is expected during arousal, as increased movements and movement bursts often associated with increased heart rate and decreased breathing rate and oxygen saturation (Joshi et al., 2016; Werth et al., 2017).

11.1.3 Sleep/non-sleep from the interviews

In general, most HCPs explained that infants typically move in cycles, where they move less (and slower) during sleep, and more during wakeful periods, before a new period of sleep again. Preterm infants typically sleep for 20-22 hours a day (compared to around 16 for term infants), with periods of sleep varying between 4-5 minutes and 40-60minutes.

Most HCPs expressed that quiet sleep is not often seen in preterm infants, where seeing quiet sleep "it's like a unicorn, it rarely occurs and it is in very short periods", in which it "sometimes looks like they are always sleeping. But some movements you can see, ok they are not in deep sleep". Nevertheless, HCPs expressed quiet sleep as very few movements (except for one neonatologist who claimed this is not the case), sometimes with the mouth open, and more incidents e.g. apneas. In addition, they see fewer startles and twitches in deep sleep, as opposed to active sleep, where startles, twitches and "sleep shocks" are commonly seen in preterm infants. In fact, some HCPs expressed that infants are sometimes quite unrestful in active sleep, showing jerky movements, extension movements, and more "disharmonic" movements.

Active and indeterminate sleep is the most common sleep stages seen in the NICU, where infants are more still than during wakeful periods, nevertheless show "grabbing movements with hands", small eye movements, "frowns on the forehead", sucking, light movements with hands/legs e.g. moving fingers or even kicking/sleep twitches. One neonatologist expressed this:

"So if a pregnant mum says, oh the baby is kicking a lot, no it's sleeping. And its sort of kicking during its sleep. Its just sort of the deep nuclei in the center of the brain giving output, you are kicking, you are doing a sleep twitch. And they have sleep twitches up to 10 000 a day. So they are just sort of constantly moving and making small movements during active sleep."

Another nurse expressed that infants in active sleep show:

"Startles (like they have a Moro reflex, for some babies, it's like their arms go out then come back in, whereas for others it might be more subdued startle), twitching, finger splay, grimacing, gagging, hiccupping, yawning sometimes, depending on the baby and their position. If they are supine their movements are much more exaggerated, while if they are on the side there might be much more subtle, because baby startles in the sleep-wake cycle is less on their back than in other positions. The number of startles occurring during a phase of active sleep depends on the baby, but it is much more likely in preterm babies. I had a baby with a gut condition so uncomfortable, who constantly startled once a minute every minute for the 10 minutes before he managed to get to deep sleep and stopped. but this is rarer."

Nevertheless, twitches and startles of older infants (post 32 weeks) might indicate that they are moving towards or away from sleep, as compared to preterm infants, where it is a sign of sleep. For both term and preterm infants, however, HCPs expressed that infants moving towards or away from sleep "will do occasional movements and then stop. The only difference would be the preterm babies, who are not as good at the sustained movements." Furthermore, a neonatologist expressed that:

"If a baby is waking up, the movements are sustained. They are cyclical, so they link with the general movements of Prechtl when you see the spill from one arm to leg to the circular movements; they are more likely to be consistent in that."

A neonatologist expressed that infants who are awake show more fluent, regular movements, where she would expect to see an "upward trend, so you start to see more regular curves and they might stop and go down but what you might see is the interval of those mountains become more regular if that makes sense." For infants who are still moving towards sleep, however, she expects to see a "rise and then go back down, so it's more of a longitudinal. If they are starting to wake up you would start to see more of a peak, it's what I would expect to see, would become much more regular. Sleep-wake behavior is absolutely cyclic. All of their behavior is cyclic."

11.2 Neurodevelopment

11.2.1 Neurodevelopment description and impact

Neurodevelopmental abnormalities are found with high prevalence in preterm infants (Craciunoiu & Holsti, 2017; Foreman et al., 2008; Sustersic et al., 2012). Typical developmental issues include motor-related problems of poor coordination, poor physical fitness, postural stability deficits, difficulties for academic achievement, difficulties for daily tasks (including self-care, learning, and attention), and increased risk of e.g. lower IQ, social and emotional adaptation and language impairment (Ohgi et al., 2003; Sustersic et al., 2012; Watson, 2010). In addition, several disorders are recognized with poor neurodevelopmental outcome. Preterm birth increases the risk of developing cerebral palsy (CP), which is a group of permanent movement disorders highly affecting movement and posture in the developing brain, appearing in early childhood (Adde et al., 2010). Early intervention will not necessarily prevent the development of CP, but it could improve functional abilities later in life (Hadders-Algra, 2004). Developmental coordination disorder (DCD) is a neurodevelopmental condition occurring in 16% of extremely preterm/low birth weight infants (Sustersic et al., 2012). DCD is associated with a lack of coordination between mental intensions and the body's ability to carry out these intentions, impacting a child's ability to perform everyday tasks, e.g. self-care, academia, and marked impairment of functional motor skills (Sustersic et al., 2012). Minor neurologic dysfunction and Hyperkinetic movement disorder are other disorders affecting the efficiency of brain processes with poor neurological outcome (Sustersic et al., 2012). These deficits (and more) could be predicted in early infancy, as many of the motor deficits in infants remain after infancy (Ohgi et al., 2003; Sustersic et al., 2012). Therefore, proper growth and development are integral to early diagnosis of health deteriorations, recognition of those at risk for later neurodevelopmental disabilities, and rapid introduction of treatment to those at most risk (Craciunoiu & Holsti, 2017).

11.2.2 Movements associated with neurodevelopmental deficits

Currently, common associations with neurodevelopment assessment in infants relates to the assessment of general movements (GMs). GMs are part of the spontaneous movement repertoire during the first half-year of life, emerging before isolated limb movements (Sustersic et al., 2012). Prechtl has found excellent accuracy in the predictive value of neurodevelopment based on the various types of GMs (as shown in Table 6) (Hadders-Algra, 2004; Nakajima et al., 2006; Ohgi et al., 2003). In fact, GM assessment has proved to be a highly sensitive and diagnostic tool for the integrity assessment of the preterm infant's nervous system (Sustersic et al., 2012). This involved detection of the presence or absence of specific movements either of one or of multiple body parts, which have successfully assisted in recognizing brain dysfunctions in infants (Cabon et al., 2019; Luca Cattani et al., 2017).

Normal GMs are classified as complex movements where all parts of the body participate, consisting of a series of gross movements of variable speed, force, intensity and amplitude (Hadders-Algra, 2004). The evaluation of movement complexity (spatial variation), assess whether the infant actively produces frequent changes in direction of the participating body parts, by continuously varying combinations of flexion-extension, abduction-adduction, and endorotation-exorotation of the participating joints (Hadders-Algra, 2004). Movement variation (temporal variation) assesses whether the infant continuously produces new movement patterns across time (Hadders-Algra, 2004). GMs with the loss of complex and variable characters either have a poor repertoire, are cramped-synchronized or chaotic (Nakajima et al., 2006).

GMs can be divided into complex, variable and fluent movements (rarely seen in preterm infants) as one extreme, and stereotyped movements such as repertoire restricted, cramped-synchronized movements as another (Hadders-Algra, 2004). These cramped-synchronized movements appear rigid/chaotic, as they are characterized by sudden contraction and relaxation of all torso and limb muscles (flexed or extended), happening almost simultaneously (Hadders-Algra, 2004; Nakajima et al., 2006). The cramped-synchronized movements are the only form of GMs considered pathological, as their presence suggests a loss of supraspinal control and frequent occurrence of these movements should be considered as definitely abnormal GMs (Hadders-Algra, 2004). Hence, an impaired nervous system results in a loss of GMs complex and variable movements, resulting in GMs becoming monotonous and poor.

GM analysis is a reliable predictor of CP, described as "A persistent abnormal pattern of cramped-synchronized GMs during the writhing period and the absence of GMs of fidgety character during the fidgety period reliably predict later cerebral palsy" (Sustersic et al., 2012). This definition specifies the reduced complexity and variation of abnormal GMs. Stereotypic arm movements (not legs), jerkiness of spontaneous movements (at term age), fidgety/jerky/clumsy movements, random uncontrolled movements, muscle spasms, and tremors (in particular shaking hands) are also associated with CP (NHS, 2017; Zahed et al., 2015). MND is predicted by abnormal fidgety movements (Sustersic et al., 2012), whereas hyperkinetic movement disorder is characterized by excessive abnormal involuntary movements. These movements can be detected by choreiform movements[27] of the extremities and abnormal mouth/tongue movements (Huntsman et al., 2008). These movements typically worsen during periods of respiratory failure and are attenuated during sleep (Huntsman et al., 2008).

Another neurodevelopmental issue is the persistence of immature movements. GM shows age-specific characteristics (see Table 7) (Hadders-Algra, 2004). GMs at a preterm age are typically of large amplitude, often high speed and accompanied by the pelvis, with a duration varying from 3 to more than 60 seconds (Zuzarte et al., 2019). As infants age, the total duration of brief body movements (<5 s) decreases, whereas the duration of longer body movements (>30 s) increases (Zuzarte et al., 2018). Hence, short bursts of simple (immature) movements such as twitches, startles and sights eventually progress into longer movements involving the entire body (Zahed et al., 2015; Zuzarte et al., 2019).

Table 6: Poor repertoire GM scoring by Prechtl

Movement item	Separation	Scores
Rotary components	Movements of neck, trunk, arms and legs separately	present, fluent and elegant (2); few rotations (1); no rotations (0).
Movement amplitude	Upper and lower limbs separately	variable, full-range (2); predominantly small range (1); predominantly large range (1); mainly medium range (1).
Speed	Upper and lower limbs separately	variable (2); monotonously slow (1); monotonously fast (1); mainly medium speed (1).
Range in Space	Upper limb only	from horizontal to a vertical plane (2); mainly horizontal, on the surface (1); mainly vertical, arms lifted (1).
Onset	Upper and lower limbs separately	smooth (2); minimal fluctuations (1); abrupt (0).
Offset	Upper and lower limbs separately	smooth (2); minimal fluctuations (1); sudden release (0).
Cramped components	Upper and lower limbs separately	absent (2); unilaterally present (1); bilaterally present (0).
Tremulous character	Upper and lower limbs separately	absent (2); unilaterally present (1); bilaterally present (0).
Fidgety movements	Neck, trunk, limbs	Normal, abnormal, absent

[27] Repetitive and rapid, jerky, involuntary movement that appears to be well-coordinated

Table 7: GMs for different age groups, retrieved 02.10.2019 from (Hadders-Algra, 2004)

GM type	Period of presence in weeks' PMA	Description
Preterm GMs	From ± 28 wk to 36-38 wk	Extremely variable movements, including many pelvic tilts and trunk movements
Writhing GMs*	From 36-38 wk to 46-52 wk	Something forceful (writhing) has been added to the variable movements. Compared with preterm GMs, writhing GMs seem to be somewhat slower and to show less participation of the pelvis and trunk
Fidgety GMs*	From 46-52 wk to 54-58 wk	Basic motility consists of a continuous flow of small and elegant movements occurring irregularly all over the body, ie, head, trunk, and limbs participate to a similar extent. The small movements can be superimposed by large and fast movements

**Writhing* and *fidgety* are also words used to describe pathological movements. Here the words denote age-specific details of normal GMs. At any GM age, the basic characteristics of normal GMs are participation of all body parts and movement complexity and variation.

In addition to GM assessment, the NBAS scale is often used to assess neurodevelopmental processes as it has a neurological/behavioral perspective, where lower motor scores suggest disorganization of behavioral systems (Brazelton, 1984; Craciunoiu & Holsti, 2017; Ohgi et al., 2003). Ohgi et al. (2003) found in his comparison study of cluster scores between mild/severe disability and a normal group, that motor cluster scores significantly lower in the mild and severe disability groups compared to the normal group. Lower motor cluster scores include motor performance, quality of movement (motor maturity and coordination), which associated with increased risk of disability at the age of five, resulting in dysfunction of the CNS and/or sensory-motor system (Ohgi et al., 2003). Assessment of Preterm Infant Behavior (APIB) is an adapted version of NBAS more suitable for premature, stressed or more fragile infants (Ohgi et al., 2003), assessing, for instance, state changes, startles, tremulousness, hand to mouth, rapidity of buildup (activity) and irritability (Brazelton, 1984). Other scales such as Test of Infant Motor Performance (TIMP) include body alignment and limb movements, while Neurobehavioral assessment of the preterm infant (NAPI) is based on motor development and sleep (Craciunoiu & Holsti, 2017). Craciunoiu & Holsti (2017) found TIMP and GMs to have promising predictive validity in predicting later neurodevelopmental outcome in preterm infants.

11.2.3 Neurodevelopment from the interviews

HCPs (specifically the HCPs trained for it) observe some aspects of infant movement during care.

Firstly, they observe whether premature infant movements persist or slowly become more fluent with age. These premature movements were expressed as uncoordinated movement patterns, where infants e.g. are unable to get out of an extension and back to fetal posture (hands and feet on the midline) on their own, or unable to get the hands up to the mouth. The youngest infants need help for this, although it is a part of the developmental patterns that they eventually manage this on their own.

A neonatologist expressed the importance of detecting (a lot of) twitches and movements during the maturation processes, as it is a positive developmental sign. Observing maturation naturally relates to age specifications, as HCPs need to interpret what is normal for each age. For instance, infants are typically more tired in some weeks as compared to others (for unknown reasons), in particular, week 34/35:

"They grow and become more mature in their movements. And then you also have the age of some weeks where they suddenly are more tired than other weeks, so often we know that ah the baby is in this week so its normal to be a bit more tired than this week. If they have been small, it comes in weeks 34 and 35, where they are a bit extra tired. I don't know why, but it is like that. But some people say it is because they are calmer in the stomach."

Second, HCPs observe whether movements are variable, fluent, and have elegant rotatory components. For example, infants should not be "cramped and show staccato movements". These "staccato movements" were explained as rigid, not fluent movements (in fact they mentioned that also preterm infants might have fluent movements as well). Nevertheless, the "staccato movements" are seen in around 1/100 infants (according to the neonatologist), hence not very often. A sign occurring move often (for disturbed development) is monotonous movements, explained as stereotypical movements that are not variable, in which many movements will repeat (not like convulsions, but that they keep doing the same thing) which is seen much more often. These movements, however, are more difficult to notice and require HCPs to pay careful attention to the infant, which is time they often don't have in daily care. In addition, so-called "bad movements" occur more often, especially when the movements are very different (very abnormal movement patterns), such as abnormal cramped-synchronized GMs.

Hence, staccato movements are easier to detect; but rare, whereas monotonous movements are more difficult to detect, nevertheless, an important sign.

12 APPENDIX C: ENCODING MATRIX

12.1 LITERATURE USED IN THE ENCODING MATRIX

Table 8: Literature - Encoding scheme

L1: Brazelton (1984) L2: Chatterje (2011) L3: Ohgi (2003) L4: Als et al. (2005) L5: L.Holsti, 2004 L6: Joshi, Kommers, et al. (2019) L7: Rosenberg et al. (2010) L8: Singh, Dutta & Narang (2003) L9: Zupanc et al. (2004) L10: Ambati et al. (2016) L11: Verstraete et al. (2015) L12: Joshi et al. (2019) L13: Van en Bruel et al. (2010)	L14: Weber et al. (2003) L15: Fairchild (2013) L16: Kudawla et al. (2007) L17: Fox et al. (2015) L18: Stone et al. (2013) L19: Fernández-Alvarez (2015) L20: Sankar et al. (2008) L21: Facini, Spagnoli & Pisani (2016) L22: Cattani et al. (2017) L23: Karayannis et al. (2006) L24: Lee et al. (2012) L25: Poblano, Marquez, & Guadalupe (2006)	L26: Stevens et al., 2014 L27: Basheer, 2015 L28: Poryo et al. (2018) L29: Huntsman et al. (2008) L30: Cabon et al. (2019) L31: L. Cattani et al. (2014) L32: Orivoli et al. (2015) L33: Peyrovi et al. (2005) L34: Hill et al. (2005) L35: Grunau et al. 2000 L36: Morison, 2003 L37: Holsti, 2005

12.2 EXPLANATION OF ENCODING MATRIX AFTER INTERVIEWS

Posture

Out of fetal posture: HCPs that mentioned that infants are unable to bring themselves back to the fetal position is also included here.

Overall activity level

Increase/Active: In the interviews, the increased activity level is what was often referred to as restlessness, where infants move more than normal, or infants move a lot. This also contains statements of inability to relax (and is often associated with an HR that remains high). This field also contains mentioning of more frequent cycles of activity (specified by some HCPs as typically 30 sec to 2 min of activity at the time), cycles of activity occur more frequently (closer together) than normal (less resting time) / more occurrences of short bursts of movement the previous X hours. In addition, “infants remain agitated despite comforting“ and agitation is included here.

Lethargy: In general, lethargy is a low activity level (absence body movement). In the table, everything mentioned related to reduced movements, reduced energy, reduced activity level, active baby becoming still, low energy, absence of movement, absence of spontaneous movements, loss of overall movements, not moving, really exhausted, diminished movements, run out of energy, no motion bursts are also included as lethargy. In the literature, lethargy is typically described as the absence of spontaneous movement, reduced spontaneous movement, decrease in movement, inactivity, reduced movement, floppiness and minimal response after tactile stimulation (Joshi et al., 2018; Rosenberg et al., 2010; Verstraete et al., 2015).

Movement patterns

Abnormal movement patterns: contains uncontrolled movements/lack of self-regulation. Abnormal movements are often defined as infants showing alterations in the quality components of spontaneous movements, consisting of reduced fluency and variability, and poor GM assessment outcomes (Prechtl, 1974).

Cramps/tremor: This also includes cramp movements where the infant pulls themselves up and out again, “like an accordion”. These “accordion movements” could be hours or around 1-2 times during a span of 20-30 seconds.

Convulsions: Described in interviews as rhythmic, repetitive, fast or slow jerky movements/ Convulsions are either generalized to the whole body, systemic, or one limb/portion or limbs, or very subtle (e.g. one hand). They were also described as sudden involuntary, violent and irregular movements.

Startles: Startles or startle reflex classifies as quick, generalized movements starting in the limbs and often spread to trunk and neck (Prechtl, 1974). Startle is a sudden contraction of many muscles of 1-2 seconds duration, followed by a rapid waning of stronger tonic activity, eventually returning to a level before the startle (sometimes a bit higher) (Prechtl, 1974). During startles, the heart rate jumps to 120-140 breaths/min, often followed by bradycardia (Prechtl, 1974). Precthl (1974) have reported a certain periodicity with an interval of about 3 minutes, and especially in abnormal infants, somewhat longer-lasting gross movements of limbs and head occur. Startles usually occurs in an individual manner, but they may also be repetitive (Facini et al., 2016). Startle reflexes are also often reflected from irregularities of respiration (Prechtl, 1974).

Head/neck

Head extension/head-bobbing: As a part of the general classification of spontaneous movements, head rotations from a lateral position to the midline and back, or to other lateral positions, in either isolation or combination with a general movement typically show slow speed, with a few seconds duration (Prechtl, 1974). From the interviews, however, head extension and head bobbing were the most obvious observed signs.

Grimace: includes eye squeeze, nasolabial frowning (furrow eyebrows), brow bulge, pulling up upper lip (nasal furrow), wide-open mouth/yawning.

Repetitive face movements: includes face twitch, lip smack, shewing, swallowing, (excessive) sucking, mouth tickling

Specific eye movements: Includes sustained eye-opening, unresponsive ocular fixation, fluttering, unfocused and uncoordinated eyes and floating eyes.

Torso/trunk

Twitching/squirming/wriggling: squirming/wriggling includes wriggling or twisting the body from side to side. A muscle twitch is defined as an uncontrolled, fine movement of a small portion of a larger muscle.

Limbs

As a part of the general classification of spontaneous movements, it is recognized as valuable to detect isolated arm and leg movements, isolated meaning in absence of other body parts moving. Speed and amplitude of movements may vary, in which a typical duration ranges from 2 to more than 10 seconds (Prechtl, 1974).

Discrete movements: finger splay, fisting, handclasp, foot clasp, hand to mouth, grasping, holding on are all defined in the NIDCAP model (Als, 2009).

Salute: Includes lifting arms from horizontal to the vertical plane, lifting arms over the head, or lifting arms over the eyes with the hands out (stop sign). Salute (stretching hands upwards) is also from the NIDCAP model (Als, 2009). This is based on preterm infants often showing restriction for alertness by demonstrating hypertonic, flexed, high guard position with fisted hands (and breathe rapidly and unsteadily while grimacing) (Als, 2009).

Extended extremities: Considered as stretched extremities in the horizontal plane, predominantly large range. The search for "preterm infant limb extension", "preterm infant extremities extension" and "preterm infant extremities extension NEC" mostly showed articles relating to the association of extended limbs and increased pain (Liisa Holsti et al., 2005). In addition to the movement of extending the extremities, there are also tonic postures of limbs (a portion of the limb stiffening) and hyperextension of extremities. This is particularly for a decerebrate posture (tonic extension of all limbs) or decorticate (flexion of upper limbs and extension of lower limbs) typically neurologically related (seizure/cerebral hemorrhage).

Repetitive extension/flexion movements: Includes: "Movements to get things away (e.g. tubes, wires)" and "Struggling through position aids"

Stretch/drown: Extension of the trunk (and sometimes arms/legs), accompanied by struggling movements in an apparent effort to move back into flexion, but unable to do so independently.

Repetitive flexion-extension movements lower limbs: Contains the comments of kicking/smashing/stamping with the legs, and pushing themselves out of the positioning aids by using the legs. In the literature, kicking movements are defined as cyclical, rhythmical lower extremity movements in infants that are seen in a supine position from birth until around 10 months of age.

12.3 VITAL SIGNS

This section firstly describes the vital signs associated with sepsis, NEC, pain and stress from the literature, before presenting a table that summarizes the vital signs related to the clinical events from the literature and from the interviews.

Sepsis: Combinations of various vital signs are found to improve the sensitivity of sepsis detection (Weber et al., 2003). Joshi et al. (2019) specifically identified an increase in dynamic respiratory range and increased respiratory instability during sepsis buildup. In addition, a decreasing trend in heart rate variability (HRV) (increased asymmetry, reduced ability to accelerate heart rate) and transient heart rate decelerations was found to reflect subclinical signatures of sepsis (Fairchild, 2013; Griffin et al., 2007; Joshi, Kommers, et al., 2019) up to 24h before suspicion of sepsis (Griffin et al., 2007). Singh et al (2003) found, in addition to lethargy, that apnea and tachycardia were the most frequent predictors of sepsis.

NEC: There have been findings of clinical cardiorespiratory systemic signs and symptoms serving as early warning signs for NEC, in which subtle changes in baseline heart rate and respiratory parameters precede the occurrence of NEC and worsen during the progression of the disease (Stone et al., 2013). The study by Fox et al. (2015) validated these findings by identifying cardiorespiratory symptoms preceding gastrointestinal symptoms, such as the development of periodic breathing, an increase in respiratory rate, apnea and oxygen desaturation. By targeting these symptoms, one can impact the severity of NEC progression (Fox et al., 2015).

Pain: Vital signs, in particular, HR increase and oxygenation saturation decrease, were also reported (Morison et al., 2003; Stevens et al., 2014). And disturbance in sleep cycles. Furthermore, Holsti (2004) mentions shifts in sleep/wake state and physiologic indices of heart rate are promising biobehavioral pain indicators in preterm infants, classified in PIPP as an increase in heart rate by more than 25 bpm compared to baseline (noteworthy, and increase of 15-24 bpm also have a high pain score). Physiological responses are also seen in oxygen saturation (7.5% or more, or 5-7.4% in PIPP), respiratory rate and blood pressure (Hill et al., 2005).

Stress: Infants who are stressed often show autonomic stress of deep, rapid respirations, and a regular heart rate without variability (Brazelton, 1984).

Table 9: Overview of vital signs associated with clinical events in the literature and during the interviews. The black numbers in the cells depict how many interviews it was mentioned in, whereas the red numbers are which articles that mention the combination.

Vital sign	Discomfort	Pain	Sepsis	NEC	Cerebral hemorrhage	Seizure	Apnea
Temperature instability			5, L15	4		L2, L9, L21, L22, L30	
Hypothermia			2, L8, L11, L15 (preterm)				
Hyperthermia			L7, L10, L15, L16 (term)				
HR baseline changes		1	2	L18	2	L2, L9, L21, L22, L30	1
Tachycardia	3, L1	7, L5, L36	4, L7, L16	6	1	1, L9, L20, L21	
Bradycardia		1	5, L7, L11, L15, L16	3	2	L9, L20, L21	1
A decreasing trend in HRV (Regular HR without variability)	L1		1, L6, L15	1	1		
Oxygen saturation drops (Hypoxemia)	L1	L34, L36	3	2, L17		1	2
Oxygen saturation increase		L34					
Respiratory distress (periodic breathing)	L4, L32		2, L10, L11, L15	L17, L18	1	L2, L9, L21, L22, L30	
(More) apneas			5 L7, L11, L15, L16, L25	3, L17	1	1, L9, L20, L21, L29	
Respiratory drops			2	1			
Hyperpnea (increased depth and rate of breathing >60 bpm)	L1, L4		1, L11	1 L17		L9, L20, L21	
Tachypnea (rapid and shallow breathing)			L11, L15				
Blood pressure (changes)			1	1			
Drop (Hypotension)			1, L7, L15		1		
Increase (Hypertension)	L1, L32			1	1	L29	
Cardiorespiratory uncoupling: More incidents / alarms / instability in vital signs		1	5 L9, L11, L15	4		L9, L20, L21	

13 APPENDIX D: USE-CASES

13.1 USE-CASES – MOVEMENT PATTERNS AND MOTION TRACKING TECHNOLOGY

HCPs were positive to technology that provides information about infant movement for several reasons. Firstly, the current vital sings monitors lack proper indications of activity level and the presence of specific movement patterns indicating possible deteriorations. Therefore, HCPs currently rely on "knowing the infant" to detect unobvious changes/abnormalities in behavior, which is difficult with the frequently changing patient population and staff (per shift) in the NICU. For instance, one nurse expressed that she has a "trend in her head" about how an infant typically moves, considering she already cared for that infant for around 3 days. Nurses taking care of an infant for the first time does not have this pattern. Second, observations are based on HCP's interpretations, which are often biased from their previous experience and perception. These interpretations are accordingly communicated to the next nurse for each shift (three shifts per 24 hours).

A neonatologist expressed that he currently has approximately 2-3 minutes of observation for each infant to determine its possible condition, and for the rest, he relies on the nurses. He expressed that "If I could have an observation of one hour, then you can see differences and progression of several things, so if I had the possibility for that, the time then would have value". In addition, a standardized, subjective indication of infant movement enables the creation of a common language, enabling HCPs to use their own interpretations, while reducing their dependency on the human factor possibly influencing the information transfer.

> *"Every nurse looks at the infant in a different way. It is intuition and experience-based, so what is noticed depends on the nurse, what patterns she recognizes. It is the human factor that is so hard to get. In addition, there is always something going on in the head of the nurses, with all the factors that can influence the response of the baby at that moment. For example, sometimes they suspect sepsis but it could also be that the infant is exhausted, e.g. after lowering respiration support. So it is good to automate and to make it more visible, which is why technology could help to also make it more standardized."*

A neonatologist expressed that "it would be fantastic if you can look back afterward and look at what are the movement patterns of these infants". To enable this, most HCPs expressed the importance of combining several signs by creating a multimodal algorithm that detects relationships. A neonatologist expressed parents as an example of this, as they typically "have a feeling" when something is off. This feeling is often correct and highly respected by HCPs, as it "must come from an unconscious combination of all their senses" such as information on monitors, (changing) behavior of infants, color, muscle tone, etc. Therefore, combining the several movement patterns from the encoding matrix in Table 3 with the vital signs depicted in Table 4 in section 12.3 in Appendix C, into a prediction algorithm introduces several use-areas for each clinical event.

"Mom's use all their senses, and usually if you ask they don't really know. So I think it's a combination. And I think this could add, at least for making up new algorithms this could really add. If you say high risk of infection, alarm, just have a look at the baby. Maybe a look at the baby alarm. And then the nurses don't have to do this, the mom don't have to tell you, but then you have the system to tell you and then it's up to us to say I think it's sepsis, a NEC or I think it's a whatever."

Automating the observations, standardizing the information and making it more visible, possibly in combination with vital signs could enable several features (use-cases). First of all, several HCPs were interested in motion-tracking to improve illness detection, in particular sepsis (N=7) NEC (N=6), including a tool to assist in whether lethargy means ill or tired. Second, sleep/wake behavior in general (N=5), whether an infant is asleep or awake (N=10), whether the infant is in active versus quiet sleep (N=5). In addition, there was a wish of a continuous state indicator to predict sleep to enable individualized care (N=9), and gain knowledge of the previous sleep behavior in order to possibly delay nursing care/recognize risks (N=9). Third, continuous comfort scoring, in particular notice stress/distress/discomfort (N=5), notice pain (N=6), distinguish pain and stress (N=2), be alerted on repeated behavior of discomfort (also after comforting) (N=2) and to get hints of the source of irritation/agitation (N=3). Fourth, the value of the overall wellbeing of the infant (N=10), recognize trends in movements, either to detect deviations from normal behavior (N=7) or to plan individualized care (N=3). This would all be useful in order to create a multimodal algorithm that could combine several parameters to e.g. distinguish comfort and extreme discomfort, or to make more effective alarms (artefact rejection) (N=2). Fifth, some HCPs were interested in receiving some sort of alerts on changes in movements, either an increase in movement (N=3), a decrease in movement (N=2), the infant being out of the positioning aids (N=1) or other potential signs of deteriorations (N=1). Detecting convulsions/seizures were mentioned (4), and signs of hemorrhage (N=1). Furthermore, some found it interesting to track maturation/development (N=3), including GMs (N=1). Apnea detection was mentioned, but more specifically for obstructive apneas and respiratory movements associated with bradycardia. These will be considered in relation to the clinical events below. Other use-cases were mentioned briefly (my max one participant for each) and will not be considered in detail in this paper. These are, for example, an overview of infants' reactions to environmental factors, a tool for parents where they receive more information about the infant, measuring emotion, monitoring movements during nursing care to e.g. to help decide on the amount of paracetamol. For research, participants (N=4) were also interested in more information about the age-factor of movements, to discover what different signs mean per age group, and what should be expected at a specific age group.

13.1.1 Illness detection

Detecting illness in infants at an early stage in the NICU is often challenging. Firstly, there are situations when no apparent signs of illness are present during an interaction or on the monitors. One nurse expressed that: “It happens that infants are at the stage of almost dying but there has been no detection of clinical signs or on the monitor”. Second, some illnesses have already progressed before deteriorations in vital signs are shown on the monitors. This is an issue since an infant that does not show obvious signs of illness during nursing care is often not checked again before 2-4 hours. During this period, the infant might have developed signs of sepsis that are unnoticed by HCPs. This increases the risk of complications and occasionally it is too late for treatment.

> *“At the point when vital signs go down and you have more apneas, bradycardias, and SpO2 dips, you are alerted, but then you are already too late, as the sepsis is already doing something to the condition of the baby. Most of the time the NICU nurses already saw something is going to happen before the vital signs changed."*

Third, there are individual differences in disease onset and symptoms. Some infants slowly show signs of illness, whereas some get ill very rapidly. As progressive bacteria can spread very fast, “you have a completely different kid within an hour”. This is a problem, as HCPs are not constantly at the bedside. Lastly, HCPs wishes to reduce the number of blood tests drawn based on the insecurity of the presence of illness, due to the risk of antibiotic resistance. One neonatologist expressed that “we have a ridiculous amount of antibiotics for the system bacteria. And we have a lot more deaths because we get too much antibiotic resistance”.

Combining various parameters preceding illness e.g. recognized movement patterns in combination with bradycardias, unusual respiratory drops or hypo/hyperthermia in a span of 24-48 hours might resolve some of the issues above. Furthermore, the combination of parameters might assist in distinguishing possible sepsis and NEC. In addition, combining parameters assist in detecting whether infants are lethargic due to illness, or other reasons. This is also valuable, as HCPs mentioned that, even though lethargy is an important predictor of illness, it might also be a result of tiredness, e.g. following stressed situations where “the energy will run out”. Even though HCPs try to determine the causes of illness/tiredness with observation, one neonatologist mentioned that they are not extremely good at observing everything.

Sepsis

Several HCPs clearly recognized issues with the current methods of (early) detection of sepsis in the NICU and were positive to technology assisting in early sepsis detection. One neonatologist expressed that “sepsis is a major killer. Put all your money on infection. That is how we save lives, that is how we make better brains”. For sepsis detection, individualized tracking is important, as one neonatologist mentioned that: “some infants are always a bit lethargic by themselves, so it is a bit harder to see” in which “your ground status is zero, is very important to recognize”. One nurse expressed the importance of a combination of parameters:

> *“Usually you combine that to the vitals, so you see e.g. when kid not moving a lot it's likely they get apneas as well because also the respiratory system responds to that. They get very tired, not able to breathe as well as before, so the combination of how the kid appears to you, but also the presence of apneas during that presence of time. Never just the movements, always a combination. Because when we think a kid gets sick its either because they get more apneas, and the combination with them moving less and less and not responding as you are used to with that baby or with babies in general. And whenever you have a kid that is just not moving as well as you are used to, but all the vitals are ok, blood pressure is fine, heart rate is fine, they don’t get more oxygen they don’t have apneas, we don’t really have a reason to start a sepsis workup where we actively check for sepsis.”*

Various methods of presenting the information was suggested. For instance, some HCPs suggested a notification that notifies HCPs that they need to watch out/be extra alert to a specific infant, as it might show signs of sepsis. One neonatologist expressed this:

> “*Most importantly is that the possibility of an objective and continuous measure of the movement of the infant. So you can see over time, hey, the movement of this infant is getting less, or getting different in quality, or and that would be very interesting to see. So if I have an overview in the morning of saturation overnight and I see then more desaturations, and I know that oh there is something going on. It would be wonderful if I have a monitor that says hey, this infant is moving less over the night. Or getting more active. Or getting more pathologic movements, or physiologic movements, or more distressing movements overnight.”*

NEC

During the interviews, HCPs expressed a wish for some notifications of the possible risk of NEC. Detection methods for the most prominent signs of NEC being lethargy and small amplitude of movements are similar to the method for sepsis. As some HCPs expressed that NEC behavior is different within and between infants, in which they cannot find any generalizations of movements predicting NEC, also here a combination of parameters is important. For instance, combining the vital sings from Table 4 in section 12.3 in Appendix C e.g. increased HR (long term), changes in HR baseline, apneas, etc. might improve reliability. The addition of age and weight could assign higher risk factors to small, preterm infants as compared to term infants. This could notify HCPs of the presence of NEC, but also reduce symptoms e.g. pain, as it costs a lot of energy.

13.1.2 Apnea detection

HCPs recognized apnea detection in the NICU as a challenge. First, HCPs mentioned that there are many false apnea alarms "because of bad algorithms".

"The apnea measure is one of the worst vital parameter measures because it is very hard to measure respiration of the baby well, a real challenge in NICU. It also depends on where you put the ECG electrodes, to get a good detection."

This is also recognized in literature, where Williamson et al. (2013) reported the likelihood of respiration-monitoring systems' contribution to apnea prediction based on information about infant movement, due to interbreath intervals estimates being impacted by movement artifacts, rather than actually breathing. HCPs mentioned that the many false alarms often risk that HCPs switch off apnea alarms, resulting in "real" apneas possibly being missed.

"I think with respect to apnea, what would be very useful is to see, because on the monitor we can see if they have a pulse drop of oxygenation saturation, but then we don't always know what made it happen because then we are too late with looking at the baby. Because the baby has done something before we see it on the monitor. And then maybe the baby started breathing again before we look at the baby, so if there had been some information that says now the baby had apnea earlier, or something like that, because if the apnea before bradycardia or the other way around is important to know to decide what to do. So that would have been important."

Second, apneic episodes often end by the time HCPs reach the infant, in which unreliable apnea alarms increase the risk of HCPs having inaccurate information about the occurrence of a true apneic even or not. This information is important for evaluating infants' wellbeing and detecting possible underlying causes e.g. prematurity, sepsis, seizures.

Movement patterns in relation to apneas were rather clear from the literature and interviews (except for some mentioning that "not all infants show the same patterns, it's too a-specific"). Nevertheless, the signs of apneas included restlessness/struggling/thrashing motions (obstructive apneas), absence of periodic breathing movements (limbs or thorax), abnormal movement patterns and arching of the back. Only the dynamics of the movement patterns were tested in the survey, where the majority associated movement patterns of apneic events occurring in an episodic fashion (short periods of movements of approximately 10-20s). Some participants (N=8) indicated that they move in short, sharp bursts. The recognized movement patterns might be implemented in automated detection methods firstly to improve timely detection (e.g. to initialize treatment) (Lee et al., 2012). Second, continuous measurements could assist in detecting the cause/differing trigger points e.g. central apneas during quiet sleep triggered by immature respiration, during pain/stress triggered as a response to the restlessness, whether it relates to feeding (as apneas are often triggered after feeding), to prematurity, or health deteriorations. The technology could, for instance, compare the (history of) apneic events to disease history, baseline measurements, and gestational age.

"Preterm infants get apneas because the brain is not developed yet. Sometimes they are sleeping so deep and then the brain forgets to give a sign to breathe. So many apneas and bradycardias are because of immaturity, but sometimes it is also because they get ill. But in general, not considering something wrong when apnea or bradycardia."

Third, the presence of body movement preceding, during and after apnea is useful as it can help distinguish central apnea from obstructive apnea (Joshi et al., 2018). Combining apnea alarms with movements, HR and SpO2 assist in distinguishing central and obstructive apneas, as central apneas are typically followed by oxygen desaturation and bradycardia as a second sign, whereas obstructive apneas have oxygen desaturation as a second sign. Distinguishing the two is interesting to know prognosis/detect the cause.

HCPs believe sensitive sensors for motion-tracking technology e.g. pressure sensors or a camera, could pick up the absence of thoracic movements during central apnea, or the limb activity associated with thoracic movements during obstructive apneas. Detecting apneas to a finer level than current practice enables more accurate apnea alarms while assisting HCPs in getting an overview of previous apneic episodes (for potential illness detection).

13.1.3 Cerebral hemorrhage detection

Detection of the repetitive movements during convulsions and distinguishing these from benign tremors is a promising method of cerebral hemorrhage detection. In addition, convulsions would be a more specific sign as compared to restlessness, as several other conditions relate to restlessness (whereas convulsions are more specifically for the brain). Lastly, HCPs believe the detection of disturbances of normal infant cycles might imply that the infant is having a (severe) cerebral hemorrhage e.g. if they constantly move/are awake, which is enabled in the multimodal prediction algorithm for detecting trends. This algorithm also enables detection of the subtle signs that HCPs find challenging to detect, to eventually notify HCPs to check for potential cerebral hemorrhage.

13.1.4 Detecting seizures

HCPs were firstly interested in technology to detect the pathological convulsions related to seizures, to act accordingly, e.g. initiate medication to terminate the convulsions, monitor the infant with EEG for further recognition off neural activity/seizures, or detect underlying etiology.

"Clinicians will miss 50% of seizures, and also declare something of seizure that is not. Difference seizure and tremors can be difficult sometimes. They have done an investigation with video sonography, which was blinded to the clinicians, and there you see that the clinicians will miss 50% of the seizures in one way. And in the other way, they will declare some things as seizure when it is not a seizure at all electrographic. So we are really bad at it as clinicians. So I don't trust myself too much with my own observations at that point, it can be really hard."

Second, they wish for technology to assist in separating pathological convulsions from benign tremors (which is currently a challenge) to reduce the number of false positives/false negatives. This is important to prevent failure or detection, but also the unnecessary medical treatment of benign tremors or healthy infants recorded with EEG.

"EEG is a big procedure for the preterm because they need a lot of rest, and using EEG disturb them a lot with putting on the electrodes and change so we get good signals. So I think video is much less invasive and not hurting the infant, so it would be much more valuable."

Third, they believe motion monitoring technology could serve as a less invasive method for monitoring seizures/convulsions, and lastly, detection methods should assist in ruling out conditions (such as meningitis) before initiating specific therapy. This is also explained by Sankar et al. (2008).

Implementation of the recognized movement patterns into algorithms for motion-tracking technology enables smart distinction of seizures, possibly requiring less analysis for cause detection. HCPs believe technology could detect pathological convulsions and distinguish these from benign tremors firstly by recognizing the rhythmic, repetitive movements, or the subtle movements e.g. with ballistography. Second, technology could include detection of the episodic movement patterns/short, sharp bursts to improve sensitivity. Correlating this with vital signs e.g. oxygen desaturation, apneas, or HR increase possibly improve accuracy, as these vital signs correlate with pathological convulsions as opposed to benign tremors. Third, HCPs suggested detecting disturbances in typical movement cycles. For instance, infants show reduced movements during periods of sleep and increased movements while awake. Disrupted cycles with constant detection of movements, however, could be a clear sign of a convulsion. Fourth, a neonatologist suggested using technology to detect and notify about "movements out of range/abnormal movements" with a "check the infant for possible cerebral hemorrhage" notification.

"Having a movement system within the normal range, or abnormal movement definitely make a lot of sense from a just check the baby out perspective. Because usually there are other signs as well like heart rate or irritation, so having these movements are out of range sensor would make a lot of sense as well. It's like a really high, and it's not very specific, because there are other ways of moving as well.

Fifth, HCPs expressed the value of technology providing them with data to inspect in hindsight, to detect whether there was a pathological convulsion and for term infants (specifically) detect how the convulsions started. This provides them with information about the epileptic insult and the related brain areas. Current methods of inspecting this are done with a camera, although only for high-risk infants (as most infants are not video recorded).

"Sometimes, we look at when it starts and how it starts. Is it starting with all the, two legs and two arms, or is it starting with only one leg or one arm. Then the other arms and then the other legs, it tells us something about what is the place of the epileptic insult. If it really starts with all the arms and legs, then it's a generalized epileptic insult. But if it only starts with 1 hand, let's say the right arm, then the problem is in the left part of the brain, and then it can be generalized to the order part of the brains and then you start with the right, then left arms and then also the legs. So it would also be useful with the term babies to know where and how it starts and how it evolves."

Considering age characteristics are important, as there is a higher chance of "repetitive, jerky movements" being convulsions (and not benign tremors) in term infants as opposed to preterm infants, due to the immature movements (benign tremors) of preterm infants. HCPs typically associated seizures in term infants to more severe consequences as compared to preterm infants. As important during the implementation phase of all applications is the method of presenting the information. A nurse suggested the "histogram function" for this application, as this is a clear presentation method she has a positive experience with, as additional alarms are unideal in the NICU. Noteworthy, some HCPs were less positive for technology to detect convulsions. They mentioned its nice to have, nevertheless, they believe it is difficult and possibly will not influence their day too much.

13.1.5 Comfort scoring

Detecting pain in infants is important not only because of the developmental issues related to pain, in which "cumulative pain means less brain", but also because it exhausts the infants and hinders their ability to show small behavioral signs that are important for HCPs to notice. Pain is currently assessed by one-off measurements of comfort scoring tools as expressed earlier in this report. Most HCPs do not typically modify their care based on the value of the comfort score, as the procedure often becomes normalized. In fact, one nurse mentioned a problem of normalized procedures being HCPs often involuntarily ignore obvious signs from infants of crying/need for attention (as she has seen this happening several times during the same day). Some HCPs also explained the current procedures as schedule-based, rather than individualized per infant. One nurse compared nursing care and history in the military:

> *"Nurses are very militarized, so we do things every hour, we do things every 4 hours, it's very much about nursing sort of has a history in military. So instead of waiting for 4 hours to do something, you would intervene when that baby indicates in distress or discomfort. Whereas a lot of nurses, typically old-school nurses or nurses who had training on the go would wait the 4 hours to do something, like the baby is fed at 4 hours, nappy change every 4 hours. Instead of*

looking at the baby as an individual they follow the schedule. Whereas this might help them recognize it an hour and a half before that because a baby's sleep-wake cycles are 57 minutes so they are likely to arouse before 4 hours. And so what we desperately teach is that if a baby is arousing and having increasing apneas and bradycardias you need to intervene, you don't leave them there and hope it's going to resolve in the next 3 hours".

HCPs wish for technology to notify them when infants are in pain, but also to notify them when infants are changing position (out of fetal posture/out of tucking mechanism/extend their extremities), as infants often show inability to get out of extension (arms/legs) on their own, which is (even in the absence of pain) not good for development. In addition, technology enables accurate transfers between shifts as explained by a nurse:

"If you actually know that there has been this pattern of pain over a longer time, if that could mean something else, it could be valuable for maybe choosing medications. And to see that e.g. the baby has been in pain the whole morning. This carries over shifts, so if it started at 5 am and then the nurse only has 2 hours left of their shift they didn't pick it up and then the next nurse doesn't determine until 1 pm. So you know that's almost 8 hours that that baby has been in pain, and it is because of the changing staff."

One nurse was very positive to technology to detect this, as she mentioned that she would being able to get an indication of comfort/stress by observing infants 24/7, as preterm infants have a repertoire of behaviors with cyclic repetition.

Furthermore, detecting long-term patterns and potential causes might enable the distinction between pain and discomfort, where:

"The biggest challenge in neonatal care is to separate discomfort and pain. The Comfortneo scale measures discomfort, but when there is a high score, it can be stress or pain".

A nurse practitioner highlighted this distinction:

"It would be extremely valuable to look inside the brain of the baby. There are MRI studies showing that an increase in pain procedures or painful situations, you lose grey and white matter in the brain. So when we are able, if we are one day able to detect pain and distinguish it from stress, treat it well, then we may be able to make the prognosis of these babies better."

In fact, he mentioned that pain might imply stress, however, stress does not necessarily imply pain:

"In terms of neuromotive development, cognitive aspects, psychosocial. E.g. extending extremities is a sign of stress or pain or both, but not necessarily present if stress and pain. I think pain is stress. But stress is not necessarily pain. I am not sure, because somewhere along the line stress may become painful, with integration of psychosocial aspects, for instance, chronic pain is influenced by stressful situations, when a person has a chronic pain disease and is very comfortable in a stress-free environment the pain may be less severe than in a stressful environment. This all interacts with how you experience pain."

By knowing the difference, however, HCPs mentioned that they could act more accordingly and make prognosis better for development:

"If they are in pain there is a need for non-pharmacological and pharmacological pain management strategies, whereas it they are distressed comfort is completely different like the baby might need to be held or changed. But if they are in pain we should be looking for the source of the pain."

Another distinction mentioned was to distinguish between chronic and acute pain, because:

"There is great work that talks about most of the babies in the NICU are in chronic pain and we don't manage chronic pain and I think that could be useful, differentiating between movement behaviors between chronic versus acute pain in babies, and can you map that that would be very useful. Because I think if you watch the babies, their effects change over time, they become almost depressed. You watch them become very flat etc."

13.1.6 Sleep monitoring

Sleep monitoring received the highest (average) rank in the survey and was often mentioned during the interviews. HCPs have demonstrated increased awareness of the importance of both the short-term impacts of sleep on infection-prevention and wellbeing and the long-term impacts of sleep on maturation/

neurodevelopment. HCPs highlighted their concern of sleep disruption and expressed a willingness to tailor their caregiving to infants' wakefulness periods, as sleep is neuroprotective. As mentioned by a nurse, recent research has shown that infants are awoken around 57% – 80% of the time spent in the NICU, due to the neonatal environment (28-36 weeks old). A neonatologist expressed the NICU as

> *"An environment of sleep deprivation because we are constantly interrupting sleep".*

Current indicators of sleep are based on vital signs, being a challenge as:

> *"Many HCPs are so task-focused that they do not look at the monitors before intervening".*

HCPs believe accurate monitoring methods can change HCP's mindset into caring for the infant when it suits the infant, rather than the clinician, in which:

> *"Diaper change should be done when the baby wants it done, not because my clock says 12 o clock and we need it done. In some units they are very good at that, to do it based on the baby, and in other units its very clock based".*

The problem, however, is that it is very difficult to determine sleep in preterm infants, and there is little data on preterm infants 24h cycle. Preterm infants show different sleep-wake behavior as compared to older infants (specifically due to the periods of indeterminate sleep, and shorter sleep cycles), and it is more difficult to determine whether the preterm infants are moving towards or away from sleep. One recognized issue is that:

> *"Preterm infants do a lot of twitching and startling, they can make noises they can squirm. And parents and staff incorrectly think that is the baby waking".*

In addition, the very preterm infants are often covered e.g. due to receiving phototherapy during the first days of life, expressed as an issue:

> *"So in the most important hectic days of their life, they are covered up. We cover the incubator; we cover their eyes, so how would you know if the baby is asleep. You wouldn't".*

Consequently, several HCPs expressed interest in motion-tracking technology to assist them in determining sleep-wake states, and to understand state development. By enabling sleep-monitoring, longer periods of monitoring infant states are necessary for sufficient descriptions of neonatal behavior, as compared to short observation periods of single sleep cycles, which might be modified by environmental, metabolic and circulatory effects e.g. food intake, as expressed by Prechtl (1974). Sleep monitoring is useful for several reasons.

Firstly, individualized sleep tracking can assist HCPs in adapting care to respect infants' sleep-wake rhythm (for non-emergency tasks). For instance, limit care to wakeful periods, adapt alarms to sleep/wake cycles, and synchronize feeding/kangaroo care to promote sleep are possibilities for improving long-term neurodevelopmental outcome (Bertelle et al., 2007; Huntsman et al., 2008; Werth et al., 2017). Tailored nursing care could provide HCPs with information about the "window of opportunity for care" based on sleep, as preterm infants being awake is "a very small window that could easily be missed" as the signs are very subtle, e.g. they do not necessarily open their eyes during wake. Knowing when infants are awake is also useful as it is a "waste of energy if infants are moving when nobody is around". A nurse mentioned that she wished to have "some kind of curve or number or color that indicates that today he was very awake and the last few days he was sleeping much more hours than usual" as it is very useful to get an overview of the history of sleep-wake. Hence, collecting objective data about sleep-wake cycles enables developing care programs for each individual infant to promote sleep and development, and ease decision-making for nursing care.

Second, the knowledge of previous sleep behavior forms a baseline for typical sleep-wake behavior, which assists in HCPs receiving objective, standardized information. Understanding infant sleep is important as it is a way of understanding infants developing brain and internal needs (Als, 1982; Foreman et al., 2008).

For instance, infants who usually sleep at certain times every night, who suddenly are active during these periods is also an important sign for HCPs to know. This is also valuable data for detecting health deteriorations, in which an overview of sleep/wake patterns enables the identification of stress/discomfort (Werth et al., 2017) and pain in infants (L. Holsti, 2004; Liisa Holsti et al., 2005; Morison et al., 2003). HCPs also associated no sleep/longer sleep onset/more movements during sleep with sepsis, NEC and cerebral hemorrhages. On the other hand, several HCPs expressed more sleep (more hours of sleep in the day) when they have sepsis or NEC, possibly related to individual differences or differences in severity of disease or duration since disease onset. Nevertheless, technology could also alert whether infants show signs of lethargy. For instance, average sleep cycles of preterm infants are around 40-60 minutes, which should be followed by some periods of more activity (awake). Infants who are asleep/very quiet for e.g. 2-3 hours is abnormal, hence, technology could alert HCPs. In fact, this threshold to the duration of sleep phases is important, as lethargy should not be mistaken for sleep. In addition, it enables the detection of sleep-related events and diseases such as apneas (Werth et al., 2017). Therefore, the activity level should be compared to previous behavior e.g. a few hours/days, where patterns of behavior could inform about typical behavior, predict infants most likely "wake time", and detect abnormalities in the cycles.

Third, knowledge of previous sleep behavior assists in knowledge transformation during nurse handovers. The three nurse handovers occurring every 24h shift currently risk the lack of knowledge about previous sleep cycles for the nurses receiving the care. One nurse expressed this as:

> *"I would love to know how the baby has been sleeping in previous hours because I take care of a baby for around 8 hours but the night before I don't know how the baby was, I was not there. And the last few days, I think it would be helpful for me if I know whether baby sleeping or awake restless. Because if I see a baby not moving in the morning that doesn't feel like waking up then I will ask myself why. Are you not feeling well or have you been moving the whole night.*

This knowledge is currently relying on proper communication from caregivers from the previous shift (verbal and reports). By having continuous information about the previous sleep behavior; HCPs are less reliant on the nurse handovers, and more able to make (their own) informed decisions based on the data. This is could be either by letting infants sleep longer in the morning (move care to a later point in time) given they were restless throughout the night, or suspect illness after showing signs of tiredness after longer periods of sleep. Hence, long-term information about previous sleep behavior enables pattern recognition (by both technology and HCPs) which could provide HCPs with important information.

Fourth, having the data also allows for changing practice in the clinic, as you can check in the data whether there are contributors for poor sleep (e.g. the light, bed space, or caregiving). HCPs were also interested in data collection/monitoring of active versus quiet sleep, as this could give some important information about infants' health state. In addition, data collection of sleep is positive from a scientific point of view for the formation of future research programs.

Approaches for monitoring sleep with motion-tracking technology should translate current approaches to the prediction algorithm. For instance, technology could provide this information by detecting infants' sleep cycles, as infants typically move less during sleep and more when awake. In addition, infants "don't make big movements when they are sleeping", which could be detected by technology. Proposed methods of sleep monitoring consist of a division of 30 seconds epochs, with state changes if the associated movements last for more than three minutes. Longer intervals between measures suggest sleep rather than wakefulness, whereas small twitches suggest active sleep (Prechtl, 1978). A neonatologist suggested using a chart in which the density of movement provides information about how many movements were present in a certain time, as he believes body movements could be more or less quantified in a time frame. By quantifying 5 to 10-minute windows of data (to have some sensitivity), he believes it would be possible to integrate movements into the other signals. This could be presented e.g. as a number or a graph, illustrating periods or more/fewer movements that indicate sleep stages.

> *"We know that sleep stages in preterm infants vary between 4-5 minutes and 90 minutes, in which a 2 or 3-hour registration show 2 or 3 stages. So from the perspective of sleep stages, varying let's say an hour, and you have some information every 5 or 10 minutes about body movement, together with some kind of HRV index, or maybe something from the camera, then maybe we are able to get some information about movement, but also about sleep."*

Furthermore, technology could enable tailored nursing care by detecting any sign of arousing the preceding two minutes and accordingly notify HCPs that they could intervene. Two minutes was assumed by some HCPs to be enough for prediction, as a nurse explained that also NIDCAP base on two minutes, as infants' state could change every 10 seconds, depending on their gestational age. A two-minute observation "doesn't seem like much but it is quite some time", as it usually enables HCPs to get some indication on whether infants are moving towards or away from sleep. Other HCPs suggested a prediction model of the next 10 minutes of sleep, while simultaneously indicating the current sleep stage. Nevertheless, whether it is 2 or 10 minutes, prediction models could inform about the approximate amount of minutes to wait for the (quiet) sleep phase to be over. This number could be updated e.g. every 2/10 minutes. Prediction algorithms might be able to detect patterns that, in the long run, could be used by the nurses for scheduling, or to provide parents with indicators of when the infant is typically awake (if this pattern is consistent), in which they could plan kangaroo care.

For this, it is useful to know the duration of infants previous sleep and wake cycle, as it could determine typical wake-duration (e.g. 8 minutes), after a period of sleep, which would be an appropriate time for nursing care (although should not rush it to finish the care). Hence, there could be a "baby is awake, it's a good moment to go check on him/her" alarm. An example of how to present this information is by using red, orange or green light on the door/floor. A red light would indicate sleep (active or quiet), please do not disturb, green that the infant is awake and it is a good time to provide nursing care/kangaroo care, whereas orange means that it is ok to go in, but if you could wait for green it is better. Other presentation mechanisms could also be used, possibly on the door, to inform parents and HCPs whether they should enter the room or wait (unless it is necessary to enter). Hence, a presentation of general sleep behavior (over time) would be useful for both HCPs and parents, enabling more family-centered care. One of the risks, however, is that the model will hinder parent involvement. This should be prevented, as parent involvement is very important for developing infants. Therefore, technology implementation should balance this. An important consideration is that full flexibility is unideal in an intensive care, as scheduling needs to suit all the different departments (radiology, surgery, NIDCAP nurses, neonatologists etc.), hence, some planning is necessary, nevertheless, technology could improve the timing of the elective tasks.

The accuracy of sleep algorithms could be improved by combining movements with vital signs. By observing the waveform trends, you could see whether HR increase/decrease of becomes more variable/stable. A neonatologist mentioned the combination of movements with RR, HR, and HRV:

> *"Then you really increase the sensitivity of your sleep algorithm. Then you are almost like a polysomnography level but you don't have an EEG. But for the rest you are ok. So I think that makes a lot of sense to add movements because with EEG we are working with dry electrodes now but I think that would be at least 5 years ahead, but motion tracking is not. It's quite easy to track movements. So a lot easier than having dry electrode sensors that are accurate. So for improving sleep algorithms, it's an obvious one."*

On the other hand, a neonatologist expressed interest in combining movements with a non-invasive way of EEG (e.g. stickers), as he would simultaneously be interested in EEG background pattern for sleep-wake.

One challenge with motion tracking technology for sleep monitoring is that there is variability both within each infant and within every gestational week. One neonatologist expressed that:

> *"Every week have a different percentage of time spent in quiet and active sleep and total duration, and I think that some babies go through cycles within 10 minutes and some in 90 minutes, so different cycles".*

Furthermore, infants' state cycles are different just after birth (e.g. more hours of wakefulness), as compared to the following days, which is an important consideration for baseline measurement. Nevertheless, the neonatologist mentioned that, as soon as the cycles are established (over time), he believes learning algorithms could still predict whether there will be a "green light" in 10 minutes. In addition, gestational age should be considered, due to the differing movements patterns and cycles. Preterm infants have poor repertoire movements, and typically, show startles and twitches during sleep, in which technology should consider the aspects of gestational age and band them based on expected gestational behavior.

Another challenge is that HCPs are not sure how sleep/wake cycles of infants will change with tailored care. This is illustrated by Bertelle el al. (2007) who reported that both QS and AS in preterm infants increased during NIDCAP application. Currently, HCPs believe preterm infants have an ultradian sleep-wake cycle (meaning that nursing care influences sleep-wake), and once we start adapting care, the cycles might also change, hence, there is a need for normalization. For instance, a neonatologist mentioned that

> *"There is research that shows that every time we wake a preterm infant, in the subsequent sleep-wake cycle they have a 30 percent increased risk of a critical event, so that means more likely to have bradycardia or a desaturation because we work them inappropriately. This will possibly change when we stop bothering them and it might need to normalize, as it might look different."*

Where he further suggested that it would be a very interesting research to compare this "new" cycle to healthy term infants (to see what a sleep-wake cycle should look like).

13.1.7 Tracking neurodevelopment

Most HCPs are aware of the risks of disrupted neurodevelopment in the NICU and positive to movement-tracking technology that can track neurodevelopment. For instance, one neonatologist expressed that CP prediction is more accurate with GM assessment as compared to MRI studies. Most NICUs use specialized programs for observations of infant development as part of the NIDCAP assessment of analyzing videotapes of high-risk infants to detect possible neurodevelopmental defects.

Current methods lack validity, firstly as it is based on single, assessments (ranging from 2 to 40 minutes), rather than investigating a continuous "pattern of recovery" from multiple assessments. Repeated evaluations are costly and time consuming for the specialized observers. Second, HCPs conducting GM assessment are required to have an additional specialization, risking a lack of qualified HCPs for assessing all infants in the NICU. Therefore, only a limited number of infants that are assessed, a selection that is based on their age (typically younger than 28 weeks) and complications they have/have had (e.g. birth asphyxia). Third, GM assessment is currently a part of research (by observing videotapes), rather than daily care. Some HCPs expressed awareness of observing GMs during care, nevertheless, they expressed that "we don't write it down, it is not in the report", and observations of GMs during care are not common practice. Fourth, the fragility and limited tolerance of preterm infants require assessment methods that prevent unnecessary intervention and potentially harmful effects of handling, as expressed by Craciunoiu & Holsti (2017).

A neonatologist with the GM assessment specialization mentioned that she believes it is useful (and possible) to create an algorithm that detects and analyze general movements and abnormal movements:

> *"It would be great if there was a way to have some sort of system, computer learning, that would take over our capacity of analyzing those general movements. And even a system that would recognize a general movement from any other movements."*

Technology offers a more standardized way for analyzing firstly whether infants show healthy complex, variable and fluent movements, or whether they show stereotyped, cramped-synchronized, "staccato" movements, as this could already give some prognosis of neurodevelopment at a preterm age.

Second, enabling technology that continuously tracks movement quality and poor repertoire GMs can detect suboptimal conditions of infants' nervous system for early selection of infants in need of follow-up, as expressed by Nakajima et al. (2006) and to detect illness. In fact, a neonatologist mentioned that you could predict 3 months of movements in one week. Infants that show abnormal movements at a preterm age could normalize after a while; nevertheless, it is good to follow up on the progress, as abnormal movements put infants into the "high-risk" group. Therefore, motion-tracking technology could assist in selecting infants for the follow-up programs based on previous behavior, rather than using gestational age as a limit.

Third, continuous monitoring is a promising tool for tracking maturation and neurodevelopment in infants, especially as "the maturation aspect of such a simple thing could be helpful". In preterm infants, you can typically see movement patterns that are "initially a mess" (24-25 weeks), which eventually develops in showing changes in density, increased fluency, and variation of movements. By tracking movements, HCPs can detect whether the brain is developing and whether the brain has developed enough. This is specifically important for BPD, as that is a risk for infants that show premature behavior longer than normal.

In fact, a neonatologist believe motion tracking can reveal a lot about neurodevelopment

> *"I think that movement is an output of basically the deep central nervous system, so as you might now, during active sleep in preterm babies especially the brain is playing its own modes, the brain is getting a lot of output, making movements. And the feedback from those movements actually build up your brain, so your cortex, your century motor cortex. So movements is just a reflection of the modes that your brain is playing."*

Therefore, he mentioned that movement tracking of preterm infants could actually follow their development:

> *"So by tracking movements of a preterm baby, you are basically following how it is getting its motor system in shape. And so I think its extremely interesting, from a research point of view but also from a logical, how the baby is growing and how the brain is developing it's extremely interesting to follow. To get an idea of the number of twitches, small movements, big movements, so just sort of saying is the brain maturing okay. Right, is it getting enough output. And then you don't need to have it like exactly, because there is a lot of movement artefact as well, like people touching the baby or moving the baby itself, but at least it's very good, it gives an overview. So how is the brain developing, how is the brain developing itself, how is it giving itself enough endogenous input. Because a lot of the movement is not conscious or reactive, its sort of the brain telling it to move. Because preterm babies sleep, the very preterm babies sleep 22 hours a day. Term babies sleep 16 hours a day. So in the NICU, the most important brain activity is sleep. That is what they are supposed to do. And during sleep, they are developing their brains. So if a pregnant mum says, oh the baby is kicking a lot, no it's sleeping. And its sort of kicking during its sleep. Its just sort of the deep nuclei in the center of the brain giving output, you are kicking, you are doing a sleep twitch. And they have sleep twitches up to 10 000 a day. So they are just sort of constantly moving and making small movements during active sleep. So I think it's one of those things that need to be monitored."*

Furthermore, a neonatologist expressed the value of checking for asymmetry for older infants, however, this is not very valuable for preterm infants, as the cortical spinal tract is not crossed 50%/50% yet (rather 90%/10%). Lastly, also for GM assessment, the age-specific characteristics should be considered.

14 APPENDIX E: INTERVIEW GUIDE

Interview guide: Semi-structured interviews for identification of clinical use of monitoring motion in the NICU

Introduction

- Thank you for taking the time to speak with me today
- Introduction of myself and the project
- The interview will take around 45 minutes (maximum 1 hour) and we at Philips would like to receive insight on your expertise and experiences in relation to infant movement. We hope that this insight can contribute to improved technological solutions by the bedside in the NICU, by improving the health and wellbeing of infants, in addition to your practice and the workflow in the NICU.
- To emphasize, we are looking for your experiences and expertise: there are no right and wrong answers.
- Naturally, you have no obligation to answer questions if you do not want to and you can always stop the interview without giving a reason. You will have the right to review, correct, or withdraw the information you have provided at any time. How to execute your rights is described in the privacy notice you have received via email.
- I would prefer to record this interview so that I can be more present during our conversation. The recording will only be used for the purpose of transcription and deleted afterward. Is that ok with you? If you are not ok with this, we can do the interview without recording.
- Do you have any questions related to the information letter or the privacy notice?
- Would you like to participate?

About the specialist

What is your profession?

- Nurse
- Neonatologist
- Other profession (related to NICU/high care for infants)

How many years have you worked in the field of neonatal care?

- Less than 2 years
- 2-5 years
- 5-10 years
- More than 10 years

Which country do you work in?

<u>Pain/Comfort</u>

Pain

- Do you notice any specific behavior of the infant when it is in pain? (if so, please specify)

- Are there any consistent movement patterns that have caught your attention when the infant is in pain?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?

Depending on the direction of the conversation, ask whether they notice (these or similar to these):

- Finger splay
- Fisting
- Hand on face
- Flexing/extending extremities
- Facial activity such as: Brow bulge, Eye squeeze, Nasolabial furrow (Contracting the area between mouth and nose)

*These examples are to direct them, in case they cannot come up with anything immediately

Comfort

- How would you determine whether the infant is feeling comfortable?
- Are there any movement patterns that imply that the infant is comfortable?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?

Stress

- How would you determine stress in infants?
- Do you notice any specific behavior of the infant when it is stressed? (if so, please specify)
- Are there any movement patterns that imply the infant is stressed?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?
- If the infant shows excessive sucking movements without anything to actually suck on, how would you interpret that?

Depending on direction of the conversation, ask whether they notice for example:

- Tremulousness (shaking/quivering)
- Startles
- Changes in focus of eyes (unfocussed and uncoordinated)
- Limp arms and legs
- Flaccid shoulders dropped back
- Fisting

*These examples are to direct them, in case they cannot come up with anything immediately

Sleep/wake states

- Do you notice any specific behavior of the infant during sleep/wake states?

- Which behavior?
- How do you determine the sleep state of the infant (e.g. whether the infant is in quiet sleep or active sleep)
- Are there any movement patterns that assist you in determining the sleep state of the infant?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?

e.g.

- Body position?
- Movements of extremities?
- Eye and facial movements?
- Regularity of respiration?
- Responsiveness to stimuli?

Other clinical events/arousal states

- Are there any other states that would provide valuable information for ensuring optimal nursing care? (e.g. that are difficult to notice by observation)
- Are there any arousal states (e.g. angry/relaxed) that would provide valuable information for ensuring optimal nursing care? (e.g. that are difficult to notice by observation)

*Depending on the direction of the conversation, I can also mention something I read in literature and ask their opinion about it, e.g. literature suggest that infants put their hand on their face when they are in pain. Have you noticed anything like that (that you remember)?

Diseases

- Are you aware of any specific behavior that links to specific diseases?
- If yes, which behavior differs from behaviors observed in the case of other diseases?
- Do you notice any specific behavior of the infant when it is ill? (if so, please specify)
- Are there any consistent movement patterns that have caught your attention when the infant is diagnosed with this illness?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?

- Are there any consistent movement patterns that have caught your attention <u>before</u> the infant was diagnosed with this illness? (please specify)

- Do you sometimes have the feeling in hindsight of an infant being diagnosed, that this specific behavior was present?
- For example, if could this particular behavior lead to earlier detection, as compared to waring for a blood test?

Sepsis/infection

- Have you ever experienced infants showing behavior that made you suspect sepsis?
- Could you please explain what kind of behavior caught your attention for this suspicion to take place?
- Which clinical signs would need to be present in order for you to consider the need for a blood culture, to check for potential sepsis? (e.g. more alarms?)
- Have you noticed any specific (changes in) movement patterns that you relate to potential sepsis? What kind of (changes in) movement patterns?
- Are these movements shown on the whole body, or more restricted to specific limbs, the torso, or smaller, detailed movements?
- Can you please describe these movements?

Depending on the direction of the conversation, ask whether they notice for example:

- Drowsiness/unconsciousness
- Chest retractions
- History of change in activity

Seizures

- Is there any specific behavior you currently use to recognize seizures?
- If the infant had a seizure, did you ever think in hindsight that the infant behaved differently?
- What kind of behavior did you notice?
- Were there any specific movements before the seizure that caught your attention?
- Have you noticed any specific behavior during seizures of infants, that could imply other complications?

- Can you easily recognize on infants' behavior whether they have a seizure, or does it happen that you figure out that an infant had a seizure later?

Apnea

- Do you see any specific movements when infants have apneic episodes, or is this only shown on the monitors?
- Did you notice different behavior of infants before apneic events?
- (e.g. would you indicate that something is wrong, or is it suddenly an alarm indicating apnea?)

Depending on the direction of the conversation, I can also mention something I read in literature and ask their opinion about it.

About neurodevelopment

- Are there any specific behavioral patterns that, according to you, would suggest a deficit in neurodevelopment of infants that may influence the future life of the infant?
- Have you noticed differences in patterns of movements as the infant matures (increasing post menstrual age)?

For example:

- Cerebral Palsy
- Attention-deficit/hyperactivity disorder (ADHD)
- Developmental coordination disorder (DCD)
- Hyperekplexia
- Minor neurologic dysfunction
- Epilepsy

Please, describe whether any movement patterns would relate to complications of neurodevelopment relating to these future disorders.

General

- What kind of behavior have you noticed in the past that is unusual for infants in the NICU?
- Are there any specific types of movements you observe in the infant that catch your attention?

Conclusions

Thanks again for your participation. Your input has been very valuable.

- Is there anything you would still like to share with us?
  Anything we might have missed in the interview?

Closing the session.

---

*The interviews are based on, but not limited to these questions. During the conversation, anything of interest that comes up will be discussed in more detail, and potentially put the base for new questions, deviating from this scheme.

* Throughout, it is good to prioritize limb/torso/body movements over just facial movements as that is much harder to capture electronically (camera/foil)

*Goal: Keep digging for information that I did not find in literature.

15 Appendix F: Survey questions

Background information

What is your professional background?

- ❍ Nurse (NICU)
- ❍ Neonatologist
- ❍ Nurse practitioner (NICU)
- ❍ Other profession related to NICU / High care for infants ____________________

How many years have you worked in the field of neonatal care?

- ❍ Less than 2 years
- ❍ 2-5 years
- ❍ 5-10 years
- ❍ More than 10 years

Which country do you currently work in?

Infant posture

1. Most NICUs use positioning aids to support preterm infants in a fetal position, as depicted in the image below.
If infants would repeatedly move out of the fetal position, it could be an indicator that ...

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
The infant is uncomfortable/stressed	❍	❍	❍	❍	❍
The infant is in pain	❍	❍	❍	❍	❍
The infant has sepsis	❍	❍	❍	❍	❍
The infant has necrotizing enterecolitis (NEC)	❍	❍	❍	❍	❍
The infant has a (severe) cerebral hemorrhage	❍	❍	❍	❍	❍

2. If the infant is lying supine with extended extremities (arms and/or legs stretched out), it could be an indicator that ...

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
The infant is uncomfortable/stressed	❍	❍	❍	❍	❍
The infant is in pain	❍	❍	❍	❍	❍
The infant has sepsis	❍	❍	❍	❍	❍
The infant has necrotizing entercolitis (NEC)	❍	❍	❍	❍	❍
The infant has a (severe) cerebral hemorrhage	❍	❍	❍	❍	❍
The infant is having a seizure	❍	❍	❍	❍	❍

3. Would you associate movements, in particular, of the <u>lower</u> limbs (either repetitive extension-flexion movements or a continuous extension-posture of the limbs) as a possible indicator of health deterioration? (More answers possible)

❑ Yes, for (severe) cerebral hemorrhages

❑ Yes, for seizures

❑ Yes, for necrotizing enterocolitis (NEC)

❑ Yes, infants that are in pain

❑ Yes, other: ____________________

❑ No

Activity level

4. Please, indicate the overall activity level of infants (gross body movements e.g. from limbs, torso, and head) in the following scenarios:

	Lethargy - the infant is very still	The infant is moving a little less than normal	Normal activity level	The infant is a little more active than normal	Restlessness - the infant is constantly moving
The infant is uncomfortable / stressed	❑	❑	❑	❑	❑

The infant is in pain	❑	❑	❑	❑	❑
The infant is having a seizure	❑	❑	❑	❑	❑
The hours leading up to a (severe) cerebral hemorrhage	❑	❑	❑	❑	❑
The hours leading up to necrotizing enterocolitis (NEC)	❑	❑	❑	❑	❑
The hours leading up to sepsis	❑	❑	❑	❑	❑

5. Based on your experience, which movement patterns are more likely if the infant:

	Continuously moving	Moving with short, sharp bursts	Episodic: mostly still but with some periods of movements (of approx. 10-20 seconds)	Normal	Other
Is in pain	❍	❍	❍	❍	❍
Is having a seizure	❍	❍	❍	❍	❍
Is having an obstructive/mixed apnea	❍	❍	❍	❍	❍

Infant pain

6. Which movements do you associate with an infant that is experiencing pain? (More answers possible)

❑ Stretch/drown (extension of the trunk (and sometimes arms/legs), accompanied by struggling movements in an apparent effort to move back into flexion, but unable to do so independently)

❑ Grimace (eye squeeze, brow bulge, and other facial expressions)

❑ Repetitive extension/flexion movement of limbs (arms, legs)

❑ Repetitive extension/flexion movements of lower limbs (legs)

❑ Flexor movements of limbs

❑ Tremors (cramps)

❑ Startles (shocks)

❑ Tongue extension

❑ Unfocussed eyes

❑ Twitches (extremities)

❑ Diffuse squirm/wriggling motions of the trunk (wriggling the torso from side to side)

❑ Arching of the back

❑ Grasping (e.g. tubes, wires)

❑ The infant remains agitated, despite comforting

❑ Other ____________________

7. According to you, an infant that is experiencing pain moves with a speed that is ...

❍ No movements

❍ Very slow

❍ Slower than normal

❍ Normal

❍ Faster than normal

❍ Very fast

8. What are the most important movement patterns to distinguish between an infant who is uncomfortable/stressed, versus an infant who is in pain?

____

____

____

(severe) cerebral hemorrhages

9. Which movements would you relate to an infant who has a (severe) cerebral hemorrhage? (More answers possible)

❑ Convulsions (sudden, repetitive jerks / muscle contractions)

❑ Head extension (stretch/push head backwards)

❑ Head bobbing (up and down)

❑ Grimace (eye squeeze, brow bulge, and other facial expressions)

❑ Stretch/drown (extension of the trunk (and sometimes arms/legs), accompanied by struggling movements in an apparent effort to move back into flexion, but unable to do so independently)

❑ Fisting hands

❑ Salute (extension of arms into midair in front of the body)

❑ Sitting on air (full extension of legs into the air)

❑ Abnormal movement patterns, such as ____________________

❑ None

❑ Other ____________________

10. When infants have a (severe) cerebral hemorrhage, they typically

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
Move fast	❍	❍	❍	❍	❍
Have convulsions (sudden, repetitive jerks / muscle contractions)	❍	❍	❍	❍	❍
Show flexion/extension movements of lower limbs	❍	❍	❍	❍	❍
Show behavior indicating that they are in pain	❍	❍	❍	❍	❍
Show behavior indicating that they are uncomfortable/stressed	❍	❍	❍	❍	❍

Diseases

11. According to you, to what extent would infants show the movements below in the hours leading up to necrotizing enterocolitis (NEC)?

	Never	Rarely	Sometimes	Often	Always
Tremors (cramps)	❍	❍	❍	❍	❍
Diffuse squirm/wriggle the trunk (wriggle the torso from side to side)	❍	❍	❍	❍	❍
Salute (extension of arms into midair in front of the body)	❍	❍	❍	❍	❍
Fisted hands	❍	❍	❍	❍	❍
Flexion-extension movements of lower limbs	❍	❍	❍	❍	❍
Movements typically related to pain	❍	❍	❍	❍	❍

12. Are there characteristic motion patterns that distinguish between the onset of sepsis versus the onset of necrotizing enterocolitis (NEC)?

❍ No, the characteristics are the same

❍ Yes, these characteristics are: ____________________

13. According to you, would infants typically show movements of small, medium or large amplitude in the scenarios below?

	Small amplitude of movement	Medium amplitude of movement	Large amplitude of movement	Other
The hours leading up to sepsis	❍	❍	❍	❍
The hours leading up to NEC	❍	❍	❍	❍
The hours leading up to a (severe) cerebral hemorrhage	❍	❍	❍	❍
Infants who are in pain	❍	❍	❍	❍
Infants who are uncomfortable/stressed	❍	❍	❍	❍

Alarms

14. Have you ever noticed whether infants have motion bursts (intermittent episodes of movement) preceding a cardiorespiratory alarm in the NICU? (More answers possible)

❑ Yes, because I think that motion artefacts often lead to alarms

❑ Yes, because motion may often precede deteriorations in vital signs

❑ Yes, I don't know why

❑ Yes, other ____________________

❑ No

Motion tracking technology

15. Assuming it was possible to automatically and continuously monitor infant motion in the NICU, how would you score the importance of the following application:
(1= not relevant, 5=very relevant.)

	1	2	3	4	5
Monitor sleep	❍	❍	❍	❍	❍
Detecting pain	❍	❍	❍	❍	❍
Detecting discomfort/stress	❍	❍	❍	❍	❍
Detecting sepsis	❍	❍	❍	❍	❍

Detecting necrotizing enterocolitis (NEC)	❍	❍	❍	❍	❍
Detecting seizures	❍	❍	❍	❍	❍
Detecting (severe) cerebral hemorrhages	❍	❍	❍	❍	❍
Detecting signs of disturbed neurodevelopment	❍	❍	❍	❍	❍
Detecting apneas	❍	❍	❍	❍	❍

16. Would you like to share any other remarks on how continuous and automated monitoring of infant motion could bring added value for infants and caregivers in the NICU?

____

____

____