INTEGRATING FAMILIES AT NEONATAL INTENSIVE CARE UNITS FOR EMPOWERING THEM AS PRIMARY CAREGIVERS: THE IMPACT OF THE PROGRAMME

RISEinFAMILY

EudraCT Number:

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Summary of Changes from Previous Version:

Version Number **Version Date**	**Affected Section(s)**	**Summary of Revisions Made**
V 0.0:	Not Applicable	First version released
V0	Summary Objectives/endpoints	Study description; timepoint for secondary assessment; study intervention; study duration Definition of grown; secondary assessment fixed at 36 weeks PMA or discharge; parent's

	Study design	psychological assessment (Qualitative surveys defined) UM is removed; AMC proposed as non-FICare intervention centre; description of the quality improvement programme (type of control, intervention sequence, random assignment of the start of the intervention,..); timing for parental psychological assessment
V1.1	Study design	Table of expected number of patients per clinical site is included
V1.2	Study design	Minor edits in study visit procedures
V1.3	Summary Study design Statistics References	Primary endpoint refined; secondary endpoints: professional selfcare-satisfaction assessment defined; study population refined Study endpoints (as above) Inclusion criteria: parents >18years (removed) Exclusion criteria: expected transfer to a non-FICare centre (<7days hospital stay) (added) Professional selfcare is described Safety section has been reduced (USAR-SUSAR removed) Section has been developed List is updated
V1.4.1	Table SoA Summary and body text Statistics	Updated Quality improvement programme/project stated throughout Sample size calculation included
V2.0	Supporting documentation References	Updated Complete references list included
V2.2	Study design	Time to start intervention in non-FICare centres is not randomized

	Inclusion criteria	Re-worded

STATEMENT OF COMPLIANCE

Sponsor will ensure that this study is conducted in accordance with the protocol, the principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and in full conformity with relevant regulations.

The protocol, informed consent form, patient's legal representative/parent's information sheet and any applicable documents will be submitted to the appropriate Ethics Committee (EC), Regulatory Authority and any other Regulatory Body for written approval according to applicable regulations. Approval by regulatory bodies of both the protocol and the consent form must be obtained before any participant is enrolled.

All substantial amendments to the original approved documents will be also sent to an appropriate EC, Regulatory Authority and any other Regulatory Body for written approval according to applicable regulations; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from trial sponsor, funding agency, and documented approval from the appropriate EC, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

Patients will not receive any economic compensation for the participation in the present study.

1 PROTOCOL SUMMARY

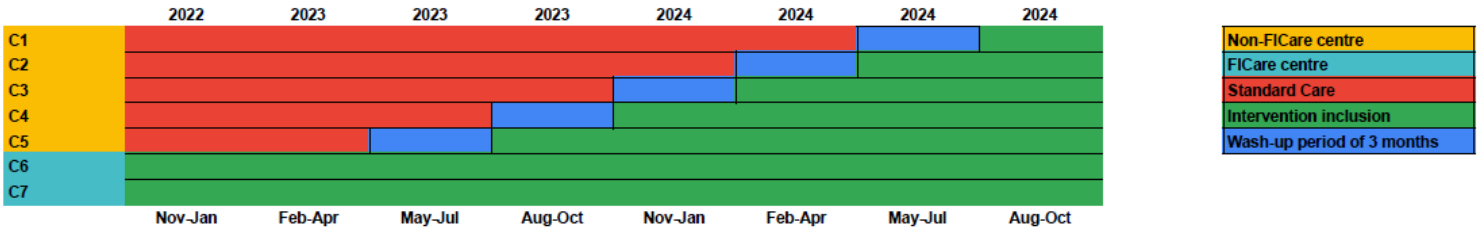
1.1 SYNOPSIS

Title:	Integrating families at neonatal intensive care units for empowering them as primary caregivers: the impact of the programme
Study Description:	International, multi-centre, pluri-cultural, stepped wedge cluster controlled trial, to demonstrate superiority of site tailored 'Family integrated care model'(FICare) [O'Brien 2018], that promotes the active participation of the parents as primary caregivers of their infants in neonatal intensive care units (NICU), versus standard NICU care delivery with regards to short-term health outcomes in high-risk newborns with prolonged hospital stay.
Objectives:	Primary objectives: ● To scale up and adapt the FiCare model (here in after RISEinFAMILY model) by including a wider geographical and sociocultural diversity and making it suitable to 2 implementation levels (basic and advanced) at a total of 7 clinical sites ● To demonstrate (short-term outcomes) that RISEinFAMILY model as compared with standard NICU care, increases the proportion of high-risk infants achieving and maintaining adequate growth pattern during NICU admission Secondary objectives: ● To evaluate the feasibility and safety of RISEinFAMILY model ● To analyse the effects on feeding patterns and maturation skills ● To address the impact of RISEinFAMILY model on shorth-term comorbidities ● To explore the effects of RISEinFAMILY model on parental psychosocial needs, empowerment and mental health ● To assess the role of RISEinFAMILY model on NICU professionals' selfcare and satisfaction Exploratory objectives: ● To analyse the effects of RISEinFAMILY model on long-term neurodevelopment ● To analyse the effects of RISEinFAMILY model on mid and long-term infant's general health

	● To estimate the cost-effectiveness of the implementation of FICare in terms of improving neurodevelopmental outcomes in preterm infants, and psychological performance in parents and clinical staff compared to the current model of care.
Endpoints:	Primary endpoints: ● RISEinFAMILY implementation: a) proportion of families completing basic and advanced training levels (observed vs expected); b) average time to complete basic and advanced training levels (observed vs expected); c) average time of kangaroo care per day (hours) ● Short-term health infant's outcomes: a) proportion of high-risk infants achieving and maintaining adequate growth patterns during NICU admission. [A] [A] Growth pattern will be defined according to Patel's method [Patel AL 2005, Cormack B 2016] that will be weekly calculated from enrolment to discharge. Secondary endpoints: ● Reported adverse event rate per 1000 patients/day ● Feeding patterns at discharge: a) proportion of infants on exclusive breast feeding; b) >50% breast feed infants; c) day of life (DOL) and postmenstrual age (PMA) to reach full enteral nutrition (>130 mL/K/day); d) DOL and PMA to complete oral feeding (nasogastric tube removed); e) DOL and PMA at discharge ● Proportion of infants diagnosed of (at 36 weeks PMA or discharge): bronchopulmonary dysplasia (BPD), oxygen dependency, severe retinopathy of prematurity (ROP) (grade 3 or need for treatment), nosocomial infection [Shane et al 2017] necrotising enterocolitis (Bell's >stage 2), moderate-severe brain injury (worst cranial ultrasound)[Plomgaard AM 2016] ● Parental needs, empowerment and psychological health: parental stress at NICU, anxiety and depression symptoms, perinatal depression (for mothers), post-traumatic syndrome, self-efficacy, maternal-to-infant-bonding and resilience ● Professional's selfcare and satisfaction: anxiety and depression symptoms, perception about parental participation, burnout, post-traumatic stress, work and wellbeing, decision-making process (only physicians) Exploratory endpoints: ● Long-term neurodevelopment: Proportion of infants who survive without neurodevelopmental disabilities at 24 months ● Mid-term infant's general health: a) Proportion of infants maintaining adequate growth pattern during the first 12 months after birth; b) proportion of infants using health system facilities after discharge (at 3, 6 and 12 months corrected for prematurity), considering hospital readmissions (number of episodes) and frequentation of Emergency Service (number of episodes)

	● Economic impact: Level of post-implementation utilization of FICare; resources and costs associated with FICare implementation; cost-effectiveness estimates compared to the current care; expected value of current implementation and expected value of perfect implementation.
Study Population:	Preterm & term neonates (and their families), admitted to NICU due to complex congenital or acquired diseases or immaturity related issues, for which a long length of stay is anticipated (i.e., at least 3 weeks) or specialized care is needed, will be eligible for screening and enrolled, providing all inclusion criteria are fulfilled and none of the exclusion criteria apply.
Description of Sites/Facilities Enrolling Participants:	7 NICUs are expected to be recruiting infants into this trial. Clinical sites will be located in Europe and Africa.
Description of Study Intervention:	This quality improvement project is designed as a stepped wedge cluster controlled trial**:** **Experimental intervention:** FICare implementation model will be demonstrated by setting 5 pilots in non-FICare-experienced NICUs from NL, TR, RO, UK, ZM (AMC, GU, CLUJ, UHS, and ZSM, partners, respectively) and 2 pilots in clinical sites who have recently implemented FICare from ES and NL (SERMAS and OLVG). **Control intervention:** A cohort of patients born at the non-FICare clinical sites (AMC, GU, CLUJ, UHS, and ZSM) from the start of the study (November 2022) to the time assigned to start the intervention. A 3-month wash out period will be stablished for staff training and site readiness.
Study Duration:	The estimated time from when the study opens to enrolment until completion of data analysis is 32 months.
Participant Duration:	It will take each individual participant a maximum of 24 months to complete all participant visits.

1.2 SCHEMA



Refer to **Section 1.3, Schedule of Activities** for assessments required at each visit and their timing.

1.3 TABLE 1 - SCHEDULE OF ACTIVITIES (SOA)

	Screening	Enrolment	Intervention	End of intervention	Shot-term endpoint assessment	Mid-term endpoint assessment	Long-term endpoint assessment
Study visit	SV	BV	IV(1)>>>IV(n)	EoI	STV	MTV	LTV
Date	x	x	x	x	x		
ICD	x						
Signed ICD		x					
Eligibility *[a]*	x						
Demographic & perinatal data *[b]*		x					
Parental data *[c]*		x					
NICU facilities *[d]*		x					
FICare profile *[e]*		x					
DOL & PMA		x		x	x	x	x
Neonatal outcomes *[f]*					x		
Task on training *[g]*			x	x			
Kangaroo (h/w)			x*				
Weight, length, head circumference		x	x	x	x	x	x
Nutrition *[h]*				x	x	X	
Maturation skills *[i]*				x	x		
AE *[j]*			x	x	x		
Reason for early discontinuation				x			
General health *[k]*						x	x
Neurodevelopment *[l]*							x
Parental questionnaires *[m]*		x			x	x	

Staff questionnaires *[n]*	

X : Indicates Mandatory Procedures that should be entered into the eCRF; X*: Indicates data entered into the eCRF if available; IV"N"= IV1, IV2, IV3, IV4, IV5, etc.*[a] section 5.1; [b] section 8.1.2.1; [c] section 8.1.2.1; [d] section 8.1.2.2; ; [e] section 8.1.2.2; [f] section 8.1.2.1; [g] section 6.2 (Table XX) and section 8.1.2.2; [h] section 8.1.2.2; [i] section 8.1.2.2; [j] section 9; [k] section 8.1.1.6 and 8.1.2.3; [l] section 8.1.1.7 and 8.1.2.4; [m] section 8.1.2.2; economic data only at discharge, section 8.3.1.2 ; [n] Psychological questionnaires pre-program implementation and at least 3 months after program implementation, section 8.2.1; economic data only after program implementation, section 8.3.1.3*

2 INTRODUCTION

2.1 STUDY RATIONALE

2.1.1 THE CONDITION TO ADDRESS

Preterm birth, defined by the WHO as a birth before 37 weeks of gestation, is a major cause of infant mortality and morbidity in developed and developing countries. Every year, about 15 million babies are born prematurely around the world, more than 1 in 10 of all newborns [Blencowe H 2012]. Preterm and very low birth weight infants (<1,500g) are at risk of developing short and long-term complications such as cerebral palsy, cognitive deficits, visual or hearing impairments, cardiovascular and respiratory diseases, gastrointestinal problems, and other conditions which can alter their life course and their capacity to work later in adulthood [Behrman RE 2010]. In addition to preterm infants, term newborns who suffer severe acquired diseases, congenital malformations, or rare diseases, also have prolonged hospital stay and, therefore, face similar burdens and challenges [Levey A 2011]. Altogether these infants can be referred to as “high-risk neonates”. Parents and other primary caregivers of high-risk neonates are in shock and suffer as they need to confront that there is a family member with an increased vulnerability. They must spend long periods in the neonatal intensive care unit (NICU) where most of them feel anxiety, stress and post-traumatic symptoms which undermine their ability to undertake normal caring roles [Bouet KM 2012]. This is a real concern considering the interdependent relationship between mother and child.

Clinical staff at NICU are at particular risk for burn-out. Professional wear for empathy is a concern among NICU personnel. They need parents in NICU. They can take a substantial role at providing direct care for their precious infants, which is essential for their early development [Bhutta ZA 2004, Ortenstrand A 2010]. However, although the concepts of family-centered care have been widely promoted, most programmes nowadays do not integrate parents as part of the care team. Hence, it is still necessary to progress beyond the humanization of care and to undertake a targeted implementation research on the best strategies leading to the active involvement of families as integral members of NICU teams.

2.2 BACKGROUND

2.2.1 WHY IMPLEMENTING THE FICARE MODEL?

The Family Integrated Care (FICare) programme [O’Brien K 2018] has been developed in a multicenter cluster randomized controlled trial, with 26 tertiary NICUs from Canada, Australia and New Zealand, comparing standard NICU care (which was mainly care by nurses) (891 infants) to FICare programme (895 infants). Eligible infants were born 33 weeks of gestation or earlier and had no or low-level respiratory support. Eligible parents committed to be present 6 hours a day, attended educational sessions and actively cared for their infant. After a 21-day period, FICare programme improved infant weight gain, increased high frequency exclusive breastfeeding and decreased parental anxiety. These findings are crucial given that postnatal growth [Tich SN 2011] is an important independent predictor of neurodevelopmental outcomes in preterm infants, and improved psychological performance in parents can definitely benefit parent-infant bonding and long-term infant’s outcomes [Woodward LJ 2014].

2.2.2 SUMMARY OF CLINICAL RESEARCH ON FICARE IN THE TARGET POPULATION

FICare was born at Mont Sinai Hospital in Toronto. O’Brien et at conducted the first pilot study on FICare model and showed that the involvement of parents in the direct care improved weight gain and increased breastfeeding rates in the preterm infants [O’Brien K 2013]. In addition, their parents had lower rates of stress and anxiety. These results were confirmed in a cluster-randomized controlled trial [O’Brien K 2018].

Subsequent studies carried out so far have shown promising positive effects on a variety of domains. Maturation profiles have been shown to accelerate with the FICare intervention as a shorter time to achieve exclusive enteral nutrition as well as oral nutrition has been shown in the preterm infants included in FICARE programmes compared to control babies [Banerjee J 2020]. Possibly aligned with that, the more individualized care provided by parents, who spent more time in the NICU, had a positive impact both on their infant's hospital length of stay, which was reduced by several days [Örtenstrand A 2010, Benzies KM 2017], and on the ability to breath autonomously, as a shorter time on mechanical ventilation was also observed [Hei M 2021; Banerjee et al 2020]. Decreased rates in late-onset sepsis, that entails other comorbidities as well as longer hospital stay, have been also reported related to FICare implementation at NICU [Van Veenendaal NR 2020, Hei M 2021].

Although most studies focus on the short-term health outcomes of preterm infants, the long-term neurodevelopment and neurobehavior of infants that were cared according to the FICare principles during NICU admission have been the focus of more recent research. Improved neurobehaviour at 18 months, consistent on lower dysregulation scores, indicating better self-regulation skills, have been reported as a result of FICare intervention [Church PT 2020]. Synnes has reported on the neurodevelopmental outcomes at 18 months of the patients participating in the FICare cluster-randomised controlled trial [O'brien K 2018] and found higher motor scores assessed by the Bayley-III Motor Scales in infants pertaining to the intervention compared to those in the control group [Synnes AR 2021].

Although reports on FICare model implementation are almost limited to stable preterm infants who had no or low level respiratory support, very recently Moreno-Sanz has described the experience and effort taken to successfully adapt and implement the FICare policies to make it suitable in the unstable, very sick extreme premature baby and other high-risk neonates suffering complex medical or surgical conditions, which provides the rationale for the generalization of the FICare model as NICU standard of care [Moreno-Sanz B 2021].

2.2.3 THE IMPORTANCE OF THE STUDY

These previous results on FICare are very promising. However, the expansion to other NICUs and other countries requires further research on the eventual barriers that may limit its adoption, especially in low and middle-income countries with very different sociocultural contexts.

RISEinFAMILY has been designed for the scaling up and adapting the FICare model for the first time in Europe and Africa. The project will go beyond the current state of the art by including a large sample size with a wider geographical diversity (7 countries), a longer post observational period (minimum 6 months, maximum 2 years follow up for the infants and their families), and a more comprehensive analysis of biological, psychological, demographic and socio-economic indicators that may affect these high-risk babies, their families and clinical staff, and thus will have significant impact on their overall physical and mental health. Cost-efficiency will be improved as well: empowerment of parents will help to reduce the hospital stay and frequentation of healthcare services after discharge. Project's results will help to spread worldwide an innovative culture for NICU care delivery that will make a lifelong difference for infants and their families.

To meet this challenging scope, the RISEinFAMILY project will follow a mixed method research-approach. The knowledge from multidisciplinary experts and the interaction between each other will be necessary and all are well represented in the project consortium.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

In the studies carried out so far, no risks associated to the intervention of parents in the direct care of their children have been reported.

In the previous studies conducted by O'Brian [O'Brien K 2013 and 2018], the number of critical incident reports is the main indicator system used to monitor safety. They describe that there was no increase in critical incidents during the implementation of FICare.

2.3.2 KNOWN POTENTIAL BENEFITS

Short and long-term benefits have been described in various studies. Regarding the former, FICare implementation has shown: improved infant's weight gain, increased rates of breast-milk feeding, and reduced parental stress and anxiety [O'Brien K 2013 and 2018, He SW 2018, Hei M 2021]; reduced time to reach full enteral nutrition and exclusive oral nutrition [He SW 2018, Banerjee J 2020]; reduced rates of relevant comorbidities in premature infants such as late-onset sepsis [Hei M 2021, van Veenendaal NR 2020]; shorter time on respiratory support and supplemental oxygen [He SW 2018, Banerjee J2020; Hei M 2021]; reduction in hospital length of stay [Örtenstrand A 2010; Banerjee J 2020; Benzeis KM 2017, van Veenendaal NR 2020, Hei M 2021]; and decreased rate of readmissions [Hei M 2021].

Focusing on the long-term outcomes, FICare implementation has shown improved motor skills and neurobehaviour at 18 months corrected for prematurity [Synnes 2021; Church PT 2020].

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

According to the experience gathered about FICare model implementation, the potential benefits on the infants and families surpass the eventual risks. A systematic approach to the assessment of the risk-to-benefit ratio deserves further evaluation in the context of the proposed research before fostering FICare as the new standard of NICU care.

3 OBJECTIVES AND ENDPOINTS

Table 2- Objectives and endpoints

OBJECTIVES	ENDPOINTS
Primary - Confirmatory Assessment	
● To scale up and adapt the FICare model (hereinafter RISEinFAMILY model) by including a wider geographical and sociocultural diversity and making it suitable to 2 implementation levels (basic and advanced) at a total of 7 clinical sites ● To demonstrate (short-term outcomes) that RISEinFAMILY model as compared with standard NICU care, increases the proportion of high-risk infants achieving and maintaining adequate growth pattern during NICU admission	● RISEinFAMILY implementation: a) proportion of families completing basic and advanced training levels (observed vs expected); b) average time to complete basic and advanced training levels (observed vs expected); c) average time of kangaroo care per day (hours) ● Short-term health infant's outcomes: a) proportion of high-risk infants achieving and maintaining adequate growth patterns during NICU admission [A] [A] Growth pattern will be defined according to Patel's method [Patel AL 2005, Cormack B 2016] that will be weekly calculated from enrolment to discharge as: [1000*(ln (weight study point 2/weight study point 1)/(date of study point 2-date of study point 1)]. For the primary endpoint study point 2 will be set at 28 days from enrolment.
Secondary - Supportive Assessment	

OBJECTIVES	ENDPOINTS
• To evaluate the safety of RISEinFAMILY model • To analyse the effects on feeding patterns and maturation skills • To address the impact of RISEinFAMILY model on short-term main neonatal diagnoses • To explore the effects of RISEinFAMILY mdel on parental psychosocial needs, empowerment and mental health • To assess the role of RISEinFAMILY model on NICU professionals' selfcare and satisfaction	• Reported adverse event rate per 1000 patients/day • Feeding patterns at 36 PMA or discharge: a) proportion of infants on exclusive breast feeding; b) >50% breast feed infants; c) day of life (DOL) and postmenstrual age (PMA) to reach full enteral nutrition (>130 mL/K/day); d) DOL and PMA to complete oral feeding (nasogastric tube removed); e) DOL and PMA at discharge • Proportion of infants diagnosed of (at 36 weeks PMA or discharge): bronchopulmonary dysplasia (BPD), oxygen dependency, severe retinopathy of prematurity (ROP), nosocomial infection [Shane AL 2017], necrotising enterocolitis (Bell's >stage 2), moderate-severe brain injury (worst cranial ultrasound)[Plomgaard AM 2016] • Parental needs, empowerment and psychological health: parental stress (abbreviated Pediatric Stress Scale for Pediatric Intensive Care Unit (PSS PICU)[Miles MS 1993], anxiety and depression (the Four Item Patient health (PHQ-4)[Kroenke 2011]; Edimburgh Postnatal Depression Scale (EPDS)[Cox JL 1987], self-efficacy (the Perceived Maternal Parenting Self-Efficacy (PMP S-E)[Barnes CR 2007], maternal-to-infant bonding (Maternal-to-Infant Bonding Scale)[Brockington IF 2006], resilience (Brief Resilience Scale)[Smith BW 2010] • Professional's selfcare and satisfaction: anxiety and depression (PHQ-4)[Kroenke 2011], Maslach burnout inventory human services survey [Schaufeli BW 1996], posttraumatic stress (PTSD-8) [Hansen 2010], Unwes-9 work and well-being survey (UWES)[Schaufeli BW 2003], SDM-Q-Doc (only physicians)[Doherr H 2017]

OBJECTIVES	ENDPOINTS
Exploratory - Supportive Assessment	
• To analyse the effects of RISEinFAMILY model on long-term neurodevelopment • To analyse the effects of RISEinFAMILY model on mid and long-term infant's general health • To estimate the cost-effectiveness of the implementation of FICare in terms of improving general health and neurodevelopmental outcomes in preterm infants, and psychological performance in parents and clinical staff compared to the current model of care	• Long-term neurodevelopment: Proportion of infants who survive without neurodevelopmental disabilities at 24 months (corrected for prematurity) [B] • Mid-term infant's general health: a) Proportion of infants maintaining adequate growth pattern during the first 12 months after birth; b) proportion of infants using health system facilities after discharge (at 3, 6 and 12 months corrected for prematurity), considering hospital readmissions (number of episodes) and frequentation of Emergency Service (number of episodes) • Economic impact: Level of post-implementation utilisation of FICare; resources and costs associated with FICare implementation; cost-effectiveness estimates compared to the current care; expected value of current implementation and expected value of perfect implementation. [B] Follow-up data collected from routine neurodevelopmental programs using all other healthcare records and parental questionnaires

4 STUDY DESIGN

4.1 OVERALL DESIGN

The co-design of RISEinFAMILY implementation model will be demonstrated by setting 5 pilots in non-

FICare non-experienced NICUs from Netherland (NL), Turkey (TR), Romania (RO), United Kingdom (UK), and Zambia (ZM) (AMC, GU, CLUJ, UHS, and ZSM partners, respectively) and 2 pilots in clinical sites who have recently implemented FICare from Spain (ES) and the Netherlands (NL) (SERMAS and OLVG, respectively).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 WHY A LARGE, CASE AND CONTROL STUDY ON FICARE?

Previous clinical investigations on FiCare have provided evidence on the feasibility of implementing this model of care in NICU setting [Moreno-Sanz B 2021] and its benefits on several health outcomes, usually focused on infants [O'Brien K 2013 and 2018; Banerjee J 2020; Örtenstrand A 2010; Benzies K. M 2017; Hei, M 2021; van Veenendaal N. R. 2020; Church PT 2020; *Synnes* 2021].

RISEinFAMILY is a PDSA (Plan-Do-Study-Act) implementation project. The strengths of RISEinFAMILY rely on a series of actions intended to bridge the "know-do" gap, to enhance the impact of the research and innovation results:

Scalability of the training into different levels (basic and advanced) according to the highest standards of neonatal, maternal and parental health that can be reached at each care unit, depending on the sociocultural context, resource allocation and NICU level of care.

Promoting an actual *shift of focus of care to the family*, *in any NICU in any context,* with a dedicated co-design strategy to cope with the barriers arising.

Knowledge transfer between participants, as advised by the WHO [WHO/EIP/KMS/2006], to overcome the knowledge-do gap in public health and to harness the power of scientific evidence to inform and transform policy and practice.

Feasibility and affordability evaluation through exhaustive economic analysis. RISEinFAMILY will include for the very first time on the FICare model a Value of Implementation Analysis (commonly used to support policy decisions on how to invest in implementation activities even in situations in which data are diverse)[Fenwick E 2008, Hoomans T 2011]. Consequently, RISEinFAMILY will be able to provide an answer to the question on whether its impact could not only improve quality of life of neonates and their families but also improve the sustainability of health systems.

4.2.2 WHAT IS THE RATIONALE FOR THE TYPE OF CONTROL?

In order to do so, a co-creation process will be run to identify the challenges related to promoting maternal and newborn health at each pilot site that needs to be considered in the implementation. To transform policy and practice at each clinical site, the project relies on an intensive and skill-based training strategy. Due to the nature of the intervention, which involves changes to unit-level provision of care (medical rounds) and interaction between participants, there is a risk of cross-contamination. Therefore, to avoid contamination of patients and staff, the stepped wedge cluster controlled trial design was selected.

The study will start at the same time at all participating sites that will continue to provide routine clinical care according to their current policies, and prospective data gathering will be accomplished. A start point for the experimental intervention will be assigned for each non-FiCare centres. Hospitals will be stratified by level of care delivered (post-intensive care or not) and number of NICU beds. Units will be allocated to a time to intervention (3, 6, 9, or 12) months, taking into account the expected time internally needed to overcome all logistics and regulatory issues with a potential impact on FICare implementation.

A 3-month wash-out period will be used for local training process and assessment of site readiness, when enrolment will be halted. After that, recruiting will continue, and the experimental intervention will be started. FiCare centres (SERMAS (ES) and OLVG (NL)) will run the experimental intervention since the start of the study, without pauses.

4.3 END OF STUDY DEFINITION

An infant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Infants and families are eligible to be included in the study only if they meet **all** of the following criteria:

Inclusion criteria for infants	**Inclusion criteria for parents**
1.Birth weight at or below 1500g or gestational age at or below 34 weeks. 2.Any other peri-neonatal condition anticipating NICU specialized care. 3. Admission for at least 7 days 4.Decision to provide full life support.	1. Willingness to spend at least 6h per day at NICU **OR** commitment to attend educational sessions 2.Active involvement in care for their infant at least a 7 day-period 3.No intellectual or language barriers[A] to understanding 4.At least one primary caregivers involved in training [B] 5.Signed informed consent

[A] If translation is needed, the language used should be understood by the trainer. For instance, if the family speaks Arab language, English and French, and most of the trainers have adequate understanding of French, the translator should use only this language in order to ensure the trainer that the translated notions are in accordance to instructions given. Clinical sites will use their own tools to overcome barriers. The purpose is to ensure that the message clearly reaches the receptor.

[B] However, it would be preferable to train more than one person in the family in care of the baby. Training may be delivered to both at the same or different moments.

Provision of signed and dated informed consent form by patient's parent/mother or legally designated representative, which can be given antenatally as described in section 5.3.

For the routine care study phase (control group) ALL the inclusion criteria for infants AND criterion #3 and #5 for parents should be full filled.

5.2 EXCLUSION CRITERIA

Patients will be excluded from the study (either during the routine care (control group) or the intervention (FICare group) phase if they meet **any** of the following criteria:

Exclusion criteria for infants	**Exclusion criteria for parents**
1.Decision not to provide full life support 2.Critical illness unlikely to survive 3.Scheduled for early transfer to another non-FICare hospital (expected hospital stay <7days)	1.Intellectual handicaps that makes difficult learning-understanding 2.Communication cannot be stablished even with translator 3.Mental, psychiatric problems or under legal supervision 4. Newborn under guardianship of social services 5.Lack of parental signed informed consent

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

By definition, this is a quality improvement project conducted on a vulnerable population, both from the perspective of the subject but also from the point of view of the parents. In many instances, preterm birth is produced suddenly, without an anticipated cause. Even in the case of antecedents supporting the risk, parents are never prepared for a preterm delivery. In the case of term newborns who suffer complex diseases the situation is similar.

This is a stressful time for parents and families. Coping with all the information provided at this early stage is difficult for parents. For this reason, a strategy for recruitment is in place to avoid overloading parents with information during the critical period after birth when they are most vulnerable:

- Prior to any enrolment, information about RISEinFAMILY project will be made public in participating hospitals by leaflets, posters and the use of modern technology.
- Whenever possible, a summary with preliminary information about the programme will be distributed to parents of potential candidates antenatally, in order to provide them with more time to think about joining the study if the baby and family become eligible after birth. Contact information for the local quality improvement team will be provided.
- Whenever possible, parents will give written informed consent antenatally after explanation of the aims, methods, benefits and potential hazards of the programme. The implications of the programme's intervention to the neonates and families enrolled should be clearly explained by the local research team as part of the informed consent process. Perinatal committees are the ideal forum to comment on potential candidates. These committees are the forum where complicated pregnancies are discussed among obstetricians and neonatologists. Appointment with eligible families can be scheduled according to the information gathered in these meetings, allowing full explanation of the RISEinFAMILY project before delivery.
- Parents that have not yet given written informed consent for the study will be approached as soon as possible after the baby is born and admitted to the NICU; and provided with the relevant parental information.

Clinical sites will be open for recruitment for the pilot on M16 (January 2023). Intermediate trial report is planned to confirm that clinical sites are aligned with the estimated recruitment rates, or to refine. This will facilitate to reach the calculated sample size.

6 STUDY INTERVENTION

6.1 OVERALL CONCEPT UNDERPINNING THE PROJECT

The involvement of families in the care of their high-risk neonates in the NICUs represents the main axis of family-integrated and family-centred care initiatives. The neonatal nurse must provide individualized care according to the conditions of the high-risk neonate and his/her family, providing an appropriate environment of care to optimize baby's development. The role of the nurse and other healthcare professionals shifts to that of a coach of parents during NICU stay in the FiCare program but maintaining a full responsibility on the infant.

The family will get the control of the upbringing of their child, both from the emotional dimension and from the operational point of view. In this sense, it is necessary to involve parents as direct caregivers, always coached and supported by the professional nursing and multidisciplinary teams working in NICUs (doctors, midwives, social workers, psychologists, veteran parents, parent associations etc.). By doing so it will be possible to progress beyond an active, safe, effective, timely and continuous high quality of care in NICUs, for the high-risk neonates and their families.

Nursing and healthcare professionals are essential in Family Integrated Care policies. In order to facilitate feasible FiCare implementation, clinical teams must be available, accessible and empathic. Team members need to acquire special verbal and non-verbal communication skills. It is their responsibility, as members of this team, to facilitate the integration of parents in the care of their child, to provide reliable information, to be aware of the family group's needs and to assign their roles. Also, in order to be able to humanize the assistance to families in the middle of a high-technology environment, it is important for all the healthcare professionals to be completely in line with this philosophy and to adapt their training methodology to the individual learning rhythm of each family.

For these purposes, a RISEinFAMILY implementation team (RISEinFAMILY-IT) is created at each clinical site. The RISEinFAMILY-IT will gather members of the local associations of veteran parents and includes a variety of professionals -social workers, psychologists, speech therapist, sociologists- and non-professional partners, in addition to NICU staff. A RISEinFAMILY clinical staff co-ordinator will be nominated.

6.2 THE CORE TRAINING PROGRAMME

The RISEinFAMILY training program is divided into two curricula: for healthcare professionals/staff (Training the trainers) and for families (Education of caregivers), the latter being categorized in two intervention levels (basic and advanced) depending on the infant care needs and parent's decision (Table 3). The following modules are identified as the minimum training contents to be delivered to foster RISEinFAMILY:

- Training the trainers: 1) understanding the boundaries of the FICare model; how to promote FICare among families; 2) psychosocial needs of families (resilience, stress and anxiety, or mourning); communication skills (assertive communication); 3) how to involve families in NICU (safe conduct in NICU environment, attachment and bonding, how to do family centered medical rounds); 4) professional self-care (burnout, compassion fatigue).
- Education of caregivers: 1) comprehensive description of the FICare model (the strengths and training methodology) and the functional and architectural structure of the NICU; 2) family self-care (stress and anxiety, resilience, or mourning); 3) learning about infants' neurobehavior, stress and pain; 4) taking part in baby care (basic level), where parents will be 'professionalized' as to become the first line care provider of their children; 5) taking part in baby care (advanced level), specific task's training for infants who require even more specialist care; 6) parents will be prepared for home; a map of the social resources available at the local setting will be provided.

0 6.3 DISEMINATION AND TRAINING AMONG NICU STAFF

A teacher education system will be used for staff training. The Chief Nurse and RISEinFAMILY-IT co-ordinator (or delegated persons) will define the mentor-assigned trainee groups and the calendar for meetings. The procedure will include face-to-face meetings , e-learning tools, or a combination of methods adapted to center facilities and organizational features. In order to accomplish the program and procedures dissemination among 90% of the NICU staff (doctors, nurses, and nurse assistants) to become facilitators of FICare. In these meetings, mentors particularly will focus on the relevance of training harmonization and the requested adherence to the contents and procedures as described on the training materials. Mentors will be available by phone or email to attend any doubt/request from their respective trainees.

The family training process relays on three cornerstones:

- Individualized theoretical and practical learning by tasks: preferably 2 family caregivers per family will be trained through face-to-face sessions at cot-side, following an individualized teaching plan adjusted to the baby's clinical condition and the wish of the parents. Once proficiency is fully accredited in a given task, the family caregiver will be certified by the training nurse (and registered) and will be allowed to do this task autonomously.
- Workshops: family caregivers are invited to attend 45-min open sessions on relevant topics of the learning contents, to express their doubts and concerns, as well as to share their experiences with other families. Three meetings per week will be programmed; selected topics will be sequentially repeated sequentially along the month, preferably every four weeks. These sessions will be held as presential , online or hybrid wise, depending on site criteria.
- Registry of teaching activities and task certifications in the corresponding logbook.

Table 3. 'Taking part in baby care': description of contents by RISEinFAMILY-IT implementation level (basic and advanced), the expected training time (*ETT, expected training time; B, basic; A, advanced)*.

Task	Level
Hand hygiene: Hand washing rules before and after interacting with their baby or his/her environment.	B+A
Physiology and monitors: Parents are trained on the general physiology principles, alarm limits, and running of the medical devices essential for baby care, i.e. incubators, thermometers, scales, or electrodes.	B+A
Intravenous lines: To identify the types of lines and the type of infusions used for intravenous administration of nutrition, medication or blood derivatives. Parents understand the general running of programming flux devices and will be able to report the nursing team any unexpected event.	B+A
Bathing: Parents take the responsibility of baby grooming without disrupting their connection with sensors and devices.	B+A
Breastfeeding: Mothers are advised and supported on how to improve their own nutritional needs during breastfeeding, breastfeeding techniques and baby positioning, how to foster milk production, manual and pump milk extraction techniques and mastitis prevention.	B+A
Other types of feeding: Parents collaborate in baby nutrition, register feeding times and volumes, double check the milk to be administered, and to apply oral sensory stimulation techniques to optimize their baby's sucking and swallowing reflexes.	B+A
Skin-to-skin & kangaroo method: Skin-to-skin contact, or kangaroo care is provided in almost any condition; parents help the nurse or do themselves the baby's transfer from cot/incubator to mother's/father's chest.	B+A
Dressing & diaper changing: Can represent a stressful event in the unstable baby. Parents receive guidelines to do these tasks in a safe manner to ensure the baby's comfort.	B+A
Oral medication: Parents know about the medications prescribed and the indication, the dosage, and the administration route. They only administer oral medications always overseen by the nursing team.	B+A
Temperature: Parents daily measure their baby's armpit temperature and report any unexpected value.	B+A

Mouth and skin care: Parents follow strict guidelines to ensure mouth and skin care in the tiny body of their babies focusing on monitoring devices connected to their skin by adhesive patches.	B+A
Interaction: This section focuses on developmental care: measures to avoid stress and promote infant's neurological and emotional development.	B+A
Positioning: Parents are trained to promote normal muscle development and movement patterns according to the baby's medical conditions.	B+A
Neurobehaviour, stress and pain: Parents understand the different neurobehavioral status of their baby to guide interactions with him/her in a confident manner. Parents are able to identify signs of stress/pain and learn how to mitigate them (non-pharmacologic analgesia, such as noise and light control, non-nutritive sucking, contention, positioning etc.).	B+A
Non-invasive respiratory support: Parents will learn to identify common breathing patterns and apnea events. Also, they are involved in supervising general items in non-invasive respiratory support, notions on supplementary oxygen and adjustments, and placement of ventilator interphase or nasal cannula. Parents understand relevant alarm events.	A
Naso/orogastric tube: Parents collaborate with the nursing team in tube positioning. Also, parents double checks the milk to be administered and register feeding times as appropriate.	A
Urinary catheter care: Parents collaborate with the nursing team in urinary catheter placement and maintenance.	A
Ostomy care: Parents take care of their baby's stoma with a special focus on skin protection when changing the pouch.	A
Daily balance: Parents evaluate and register body and diaper weight, total daily fluid intake, fontanelle and skin status, and vital signs.	A
Invasive respiratory support: Parents support their infants while nurses are doing respiratory procedures such as the amount of supplementary oxygen and other basic principles, adjustment of ventilator connectors, or to understand relevant alarm events.	A

7 STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

A participant may be withdrawn from the study at any time at the request of his/her parent(s) or may be withdrawn at any time at the discretion of the investigator or sponsor for safety or administrative reasons.

The last data should be collected at the time of study discontinuation (EoI visit, section 1.3, Table 1 SoA) and the reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled follow up visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the centre for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 RISEINFAMILY PILOTS: IMPLEMENTATION ANALYSIS (FEASIBILITY) AND IMPACT ON INFANT'S HEALTH (EFFICACY ASSESSMENTS)

The following sections describe all procedures and evaluations to be done as part of the study to support the determination of efficacy as per the primary and secondary objectives. Section 8.1.1 discusses procedures directly linked to the sequence of events during the study visits, while section 8.1.2 describes the actual procedures/evaluations to be conducted during these visits.

The specific timing of procedures/evaluations at each study visit is described in Section 1.3, Schedule of Activities (SoA). Detailed information is further provided in the corresponding Standard Operating Procedure (SOP) documents mentioned in section 8.1.2.

8.1.1 STUDY VISITS PROCEDURES

8.1.1.1 SCREENING VISIT (SV)

During the Screening Visit (SV), potentially eligible infant-family dyads are screened for inclusion/exclusion as soon as possible, either before or after birth.

Strategies for recruitment outlined in section 5.3 and the informed consent process described in section 11.1.1 are followed during the screening and enrolment of patients into the study, using specially designed Informed Consent Documents (ICD).

8.1.1.2 ENROLMENT: BASELINE VISIT (BV)

If the inclusion criteria is met, and there are no reasons for exclusion, the infant-family dyad is then enrolled into the pilot. The RISEinFAMILY training tools are provided to caregivers. At this point the Screening Visit finishes and the Baseline Visit (BV) parameters outlined in section 8.1.2.1 below are assessed. The study intervention should be initiated straight away after the Baseline Visit.

8.1.1.3 INTERVENTION: PARENTAL TRAINING BY TASK AND INFANTS' GROWTH PATTERNS (IV"N")

The study intervention is initiated. Preferably, two family caregivers per family will be trained through face-to-face sessions at cot-side, following an individualized teaching plan adjusted to the baby's clinical condition and the wish of the parents. Once proficiency is fully accredited in a given task, the family caregiver will be certified (and registered) and will be allowed to do this task autonomously.

During the pilot, weekly visits (IV 1-n) will be held by members of the RISEinFAMILY-IT. During these rounds, direct contact with families currently involved in training will be stablished. Parents will be invited to report any query, doubt or complains about the program. The progress of training and certification registry will be assessed and entered into the eCRF (Feasibility primary outcome).

The 1st primary health endpoint will be assessed at regular weekly visits (IV 1-n) where weight, length and head circumference will be measured and entered into the eCRF.

8.1.1.4 END OF INTERVENTION ENDPOINT CLINICAL ASSESSMENT VISIT (EOI)

The study intervention ends when the infant is discharged home or transferred to a non-FICare center. However, intervention (parental training) could be prematurely interrupted due to several reasons, such as parental decision, pandemic impeding or limiting parental visits, among others. Therefore, a separate visit is settled.

In the case of early discontinuation of the study intervention, the reason should be entered into the eCRF.

8.1.1.5 SHORT-TERM ENDPOINT CLINICAL ASSESSMENT VISIT (STV)

The secondary health endpoints will be assessed at 36 weeks PMA or discharge, whatever comes first. The infants postnatal age, PMA and date will be entered into the eCRF as well.

8.1.1.6 MID-TERM ENDPOINT CLINICAL ASSESSMENT VISIT (MTV)

The outcomes about general health and growth profile will be recorded at 3, 6 and 12 months, corrected for prematurity, once the infants are discharged home or transferred to a lower-level neonatal unit.

8.1.1.7 LONG-TERM ENDPOINT CLINICAL ASSESSMENT VISIT

We aim to collect follow-up data on as many children as possible by including data from routine neurodevelopmental follow-up programs, utilizing all other health care records from the age of at least 6 months. Formal evaluation is programmed at 24 months (corrected for prematurity), that is beyond the scope of the project's lifetime.

8.1.2 BASIC EVALUATIONS

The procedures and evaluations described in this section will be undertaken by all NICUs participating in the clinical trial according to the timing described in the SoA table (Section 1.3).

8.1.2.1 MEDICAL HISTORY

The following data will be captured from the participant's clinical records:

- Demographic data: date of birth and gender
- Maternal obstetric data: Antenatal corticosteroid use (complete course); Type of delivery; Any other relevant condition/medication.
- Parental (trainees) data (both): Age, type of family (mono- or bi-parental), relationship status among trainees (couple, type of relatives, friends), number of additional children, income, educational level, distance home-NICU, ethnicity, previous NICU experience, wish to breastfeed infant.
- Perinatal data: birth weight, gestational age; multiple (order); SNAPPE-II score [Fenton 2013]; 5 min Apgar score
- Intervention data: DOL and PMA at enrolment; weight, length, head circumference and Z-score at start of intervention
- Neonatal outcomes (at 36 weeks PMA, discharge or transfer, whatever comes first): overall mortality; days on mechanical ventilation (invasive/non-invasive); days on supplementary oxygen; need of surfactant; cUS main diagnoses (at 36+/-4w)[Plomgaard AM 2016]; Necrotising enterocolitis (Bell stage 2 or more) or bowel perforation; bronchopulmonary dysplasia (oxygen dependency at 36 week' gestation); oxygen dependency; nosocomial infection (use of antibiotics for at least 5 days regardless of negative or positive blood culture); stage 3 retinopathy of prematurity (ROP) or treatment; ECMO therapy; discharge date, discharge type (home, transfer to other hospital).

8.1.2.2 FICARE INTERVENTION

NICU characteristics and RISEinFAMILY training profile:

- NICU facilities: single family room; rest space or sleep room for parents; reclining chairs at bedside; free parking or transport vouchers.
- Components of the RISEinFAMILY training team (include all or any): doctors, nurses, nurse assistants; social workers, psychologists, occupational or speech therapist, veteran parents

The following data will be prospectively recorded until discharge/transfer (whatever comes first):

- Task name, date of training start, date of certification
- Weekly average time (hours/day) of Kangaroo care
- Weekly weight, head circumference and height
- Maturation skills: Time -day of life (DOL) and postmenstrual age (PMA)- to reach full enteral nutrition (>130 mL/Kg/d) & DOL and PMA to complete oral feeding
- DOL and PMA at discharge
- Nutrition: Type of feeding at discharge (only formula, at least 50% breastmilk, 100% maternal milk , or breastfeeding)
- Reported adverse event rate per 1000 patients/day
- Parental psychosocial needs, empowerment and mental health (questionnaires at start of enrolment, at discharge and at 3-6 months after discharge), number and type (presential or online) of workshops attended

8.1.2.3 MID- AND LONG-TERM GENERAL HEALTH

The following data will be prospectively recorded after discharge:

- weight, head circumference and height at 3, 6, and 12 months (corrected for prematurity)
- Type of feeding (only formula, at least 50% breastmilk, 100% breastmilk) at 3, 6 and 12 months
- Hospital readmission (diagnosis and age)
- Frequentation of Emergency Service

8.1.2.4 LONG-TERM NEURODEVELOPMENT

The follow up will be continued up to 24 months corrected for prematurity

- Weight, head circumference and height
- Neurodevelopmental impairment defined by validated test (-1SD; -2SD; normal)
- Hearing loss requiring amplification
- Blindness (corrected visual acuity less than 20/200)
- Cerebral palsy: a pattern of abnormality on neurological examination recognisable as cerebral palsy and functional impairment compatible with level 2 or higher on Growth Motor Function Classification System [Palisano RJ 2008]
- Parental questionnaires (PARKA-R)[Johnson S 2019]

8.2 THE ROLE OF RISEINFAMILY MODEL ON NICU PROFESSIONALS

8.2.1 STUDY VISITS PROCEDURES

This questionnaire dedicated to NICU professionals will be filled in by a given person twice: first time, before FICare implementation at his/her institution; second time, at least 3 months after FICare implementation at his/her institution.

In centres where FICare is currently routine of care (SERMAS and OLVG), only one time will be filled in.

The following data will be prospectively recorded from professionals:

- Socio-demographic data, work-related data, PHQ-4 questionnaire (anxiety and depression), perception about parental participation, MBI-HSS (burnout), PTSD-8 (posttraumatic stress), UNWES-9 work (wellbeing), SDM-Q-Doc (decision making process only for physicians)

8.3 ECONOMIC IMPACT OF RISEINFAMILY MODEL IMPLEMENTATION

8.3.1 STUDY VISITS PROCEDURES

8.3.1.1 NEONATES

The following data will be recorded:

- Number of days in hospital.
- Number of days on different levels of care (intensive care, high-dependency care, specialist care, normal care
- Daily cost of care per level
- Hospital readmissions (number of episodes)
- Frequentation of emergency service (number of episodes recorded since the las visit)

8.3.1.2 CARERS

The following data will be recorded:

- Personal expenses questionnaire: siblings on care, relation to the newborn on care, average hours/day on care, overnight stay at hospital/nearby, payment for overnight stay (amount), travel to hospital for care (days/week, expenses/travel), other expenses and costs (listed), other dependents under your care, any help for dependents, additional costs for helpers, other expenses (costs),
- Costs of training materials for carers (brochures, laptops, mobile devices,)

8.3.1.3 STAFF

The following data will be recorded:

- FICare Training Questionnaire for instructors: job title, pay range, training sessions (number attendees, duration, time spent on preparation, travel expenses associated to training,
- FICare Delivery Questionnaire: job title, pay range (5 categories), training received (hours), average daily hours FICare on ward, average daily hors on FICare documentation, other FICare-related duties (time)
- Cost of training materials for staff (brochures, laptops, mobile devices…)

9 ASSESSMENT OF SAFETY

9.1 ADVERSE EVENTS AND REACTIONS

Serious adverse events will not be individually reported but will be part of the data collected as part of the assessment of benefits and harms. Due to the nature of the intervention, which does not concern a medical drug and does not propose extra risk to the infants and parents, implementation of a Data Safety Monitoring Board is not deemed necessary.

9.1.1 DEFINITIONS

Adverse Event (AE):

Any undesirable medical event occurring to a participant during a clinical trial, such as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporally associated with the study intervention, whether or not considered related to the trial intervention.

This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the start of the trial intervention.

As there are no extra risks for participants (parents, infants nor healthcare professionals) related to the quality improvement programme, dispensation for the reporting of AEs is requested.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR):

Any untoward medical occurrence related to the trial intervention that:

- Results in death,
- Is life-threatening. (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

As there are no extra risks for participants (parents, infants nor healthcare professionals) caused by partaking in the study, dispensation for the reporting of SAEs is requested.

9.1.2 ADVERSE EVENT REPORTING

The patient population may include a seriously ill group. Most adverse events may be of a serious nature with or without the RISEinFAMILY trial intervention, and a very high proportion of serious adverse events is expected. It is therefore not feasible, nor meaningful to record and report all adverse events.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Primary Endpoints:

1. Adaptation of the FICare model to cultural background and clinical site is feasible: The proportion of families completing basic and advanced training levels and the average time to complete individual training by task is within the expected rates.
2. Short-term infants' outcomes: The proportion of high-risk infants achieving and maintaining adequate growth patterns during NICU admission using the Patel's growth velocity method [Patel AL 2005]. For the primary endpoint, differences in weight gain between the intervention (FICare) group and control (routine care) group will be weekly assessed from enrolment until discharge.

10.2 SAMPLE SIZE DETERMINATION

No previous study has assessed the effect of FICare intervention on growth velocity expressed in g/Kg per day. Therefore, for sample size calculation in the RISEinFAMILY project, we will follow one of the most recent studies evaluating the effect of individualized breast milk fortification on weight gain expressed in the same units [Rochow N 2021]. In this study, based on their own data obtained in a pilot and other literature data, the authors assumed 1.8 ± 3.1 g/Kg/d as a reasonable and clinically meaningful difference in weight gain. With a total N of 103 (experimental group N = 52, control group N = 51), they found a difference in the weight gain of 1.9 g/Kg/d and a standard deviation of 2.5 g/Kg/d.

Using this information, we calculated the minimum size for the intervention (FICare) and the control (standard care) group in RISEinFAMILY study. Our null hypothesis is no impact of FICare and, as a consequence, the mean of the weight gain in both the intervention and control groups will be the same. Our alternative hypothesis is a difference in the mean weight gain between FICare and control group of at least 1.9 g /Kg/d [Rochow N 2021]. We impose a type I error (probability of rejecting the null hypothesis when it is true) of 5% (α=0.05), and a type II error (probability of not rejecting the null hypothesis when it is false) also of 5% (>0.05), which provides a statistical power of 95%. The minimum sample size for intervention and control groups is given by:

$$n_i = 2 * \left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 \left(\frac{\sigma}{\delta}\right)^2$$

Where:

- n_i is the sample size of the intervention and control group.
- $z_{1-\alpha/2}$ is the value from the standard normal distribution holding 1- α/2 below it. In the case of α=0.05, $z_{1-\alpha/2} = 1.96$
- $z_{1-\beta}$, also comes from the normal distribution. For a statistical power of 95% (>0.05), $z_{1-\beta} = 1.645$
- σ is the standard deviation of the weight gain. In our case, $\sigma = 2.5$
- δ is the difference in the mean of weight gain between the intervention and control group that we expect to obtain. In our case, $\delta = 1.9$

Following the formula, $n_i \geq 46, which\ leads\ to$ at least 46 children in the intervention (FICare) and other 46 children in the control (standard care) group.

The Rochow et al study [Rochow 2021] took place at only once center. We have no reason, *ex ante*, to believe that the impact of FICare in the various participating clinical sites may be different. However, we plan to perform cluster analysis of the impact of the program, in which we consider each clinical site as a cluster. To achieve that goal, a sample size of at least 46 children in each group per center would be needed. With this approach, we aim to provide evidence of whether clinical sites from a variety of countries with different social and cultural background obtain the same or a different distribution (mean and standard deviation) of weight gain according to FICare intervention.

We will collect weekly data that will be assessed every two months in order to check whether our assumption in terms of standard deviation of the weight gain holds in all clinical sites or to identify in which ones it does not. The goal is to be able to correct any deviation from the initial expected sample size needed, both in the intervention and control group per health center.

10.3 POPULATIONS FOR ANALYSES

The primary analysis will be conducted in the intention-to-treat (ITT) population including all enrolled patient-family dyads who received at least one task training according to protocol procedures.

10.3.1 GENERAL APPROACH

Descriptive statistics will be recorded for each group with mean, median and standard deviation for numerical variables and absolute and relative frequencies for categorical variables. 95%-confidence intervals (CIs) will be provided. Comparisons between control and intervention group will be performed using chi-square tests for categorical variables, analysis of variance for normally distributed continuous variables, and Mann-Whitney or Kruskal-Wallis tests for non-normally distributed continuous variables.

Through a mixed-methods research approach and techniques both, quantitative and qualitative, the following impacts will be evaluated:

- Infants health will be evaluated and compared: i) Within-NICU comparison: in the case of those partners who had not implemented FICare before (AMC, GU, CLUJ, BSUH, ZSM), with their own dataset before implementing FICare at their respective clinical site; ii) Between-NICUs comparison: prospective datasets from already trained FICare centers (SERMAS (ES) and OLVG (NL)), versus the new datasets from the other 5 clinical sites' pilots, to assess the effect of "expertise" on outcomes.
- Socio-economic sustainability: Health economics analysis based on the value of implementation framework [Fenwick E 2008, Hoomans T 2011] will be conducted to assess the cost-effectiveness of RISEinFAMILY implementation strategies. The difference between the total net benefit of perfect adoption and the total net benefit of current implementation will generate expected value of perfect implementation (positive values would characterize cost-effective implementation strategies). The analysis will also allow identifying differences in delivering RISEinFAMILY in different countries/health care settings.
- Psychological assessment of experiences collection of either the NICUs staff and the families enrolled in the pilots. Gender differences will be explored in relation to socioeconomic and cultural background.

10.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

For our primary hypothesis we will compare infant standardized weight gain velocity between the two groups over the four-weeks study period using generalized linear mixed modelling (GLMM). For our primary outcome, we will compare infant standardized weight gain between the two groups over the study period defined as change in Patel's growth pattern measured weekly from enrolment until day 28 post-enrolment, testing an interaction term

between group and post-baseline weight measurements. We will adjust for additional covariates using a hybrid approach, forcing in known confounders of gestational age and study site and using backwards stepwise selection to retain covariates that contributed p<0.1 to the final model from potential confounders. Additionally, we will conduct sensitivity analyses adding in weight measured at discharge.

10.3.3 ANALYSIS OF THE SECONDARY AND EXPLORATORY OUTCOMES

Important prognostic variables are centre, sex and gestational age, or main neonatal diagnosis. These will be used as additional independent variables in key secondary logistic regression models for secondary subgroup analysis.

Further subgroup analysis will be conducted in line with the primary analysis, where the endpoint is dichotomous. For continuous endpoints similar modelling strategies will be used, but instead of logistic regression linear regression models will be used.

10.3.4 HEALTH ECONOMICS ANALYSES

The cost-effectiveness analysis of the FICare implementation will be carried out using recommended methods [Baltussen R 2003, Husereau 2013, Ramsey SD 2015]. A decision-analytical model [Briggs 2006] will be developed and populated with costs and effectiveness data from the pilot studies. For each FICare implementation site the cost-effectiveness of the intervention will be estimated as follows:

$ICER = \Delta C / \Delta E$

where:

ICER - incremental cost-effectiveness ratio.

ΔC - difference in mean costs for post- and pre-intervention.

ΔE - difference in mean effectiveness outcomes for post-and pre-intervention.

A one-way sensitivity analysis will be performed to evaluate the uncertainty associated with variation in costs and outcomes. A probabilistic sensitivity analysis will be undertaken to address the joint uncertainty in costs, probabilities and effectiveness outcomes using Monte Carlo simulations. Cost-effectiveness planes and cost-effectiveness acceptability frontiers will be constructed to visualize the results of the cost-effectiveness analysis [Briggs A 2006, Weinstein MC 2003, Ades AE 22006].

The expected values of actual and perfect implementation will be estimated using the Net Monetary Benefit (NMB) approach [Walker S 2013].

The Expected Value of Current Implementation (EVCI) will be estimated as follows:

$EVCI = N*(\sigma - \rho)*NMB$

The Expected Value of Perfect Implementation (EVPI) will be estimated as follows:

$EVPI = N*(1 - \rho)*NMB$

where:

1 – optimal utilization.

σ – utilization following implementation activity.

ρ – current level of utilization.

N – size of eligible populations (neonates/caregivers).

NMB – mean net monetary benefit per participant.

The cost-effectiveness and the value of implementation analyses will be conducted for the seven neonatal units involved in the study: UHS (UK), SERMAS (Spain), AMC and OLVG (Netherlands), GU (Turkey), CLUJ (Romania) and UZM (Zambia). The NMB will be calculated using the health care system willingness-to-pay threshold corresponding to the current cost of neonatal care in the NICU.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention and procedures are given to the parent/ patient's legally acceptable representative and written documentation of informed consent is required prior to starting intervention.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator (must be suitably qualified and experienced), and under the Investigator's responsibility, should fully inform the parent/ patient's legally designated representative of all pertinent aspects of the study, including the written information given approval/favourable opinion by the Ethics Committee. Templates of parent information and informed consent documents (ICD) are presented separately. The templates have been designed in collaboration with parent groups and the European Foundation for the Care of Newborn Infants (EFCNI). Each participating clinical site will adapt the templates to produce versions for their respective country submission to the regulatory authorities.

Prior to a patient-family dyad's participation in the clinical trial, the written ICD should be signed, name filled in and personally dated by the parent/ patient's legally designated representative, and by the person who conducted the informed consent discussion and recorded on the infant's clinical records. A copy of the signed and dated written ICD will be provided to the patient. The original signed form will be retained at the study site.

The parent/ patient's legally designated representative will be allowed as much time as wished to consider the information, and the opportunity to question the investigator or other independent parties to decide whether they will participate in the study; and must have the appropriate information presented in an understandable way and in a format suitable to their needs.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be temporarily discontinued or prematurely terminated if the sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study site participation may be discontinued if the sponsor, the investigator, or the ethical review board of the study site judges it necessary for any reason.

11.1.3 CONFIDENTIALITY AND PRIVACY

The study staff will ensure that the participant´s anonymity is maintained. The participants will be identified only by a participant code on the eCRF and any electronic database.

All documents will be stored securely and only accessible by study staff and authorized personnel.

Applicable regulations for storage, transmittal and disclosure of patient information will be followed at all times. The study will comply with the Data Protection Legislation in each country.

Following formal admission to the study, patient data will be recorded in the hospital case record in the usual way including the circumstances of their entry to the study. Additionally, data will be held in case report forms (eCRF). These files will be identified by a study code, date of birth and participant code only.

Representatives from the Sponsor and from the regulatory authorities will be given access to the records that relate to the study. They will have full access to the anonymous eCRFs for the purposes of data validation. Results of the study may be communicated at scientific meetings and will contribute to the scientific literature. At no time, will this be done in such a way that an individual patient may be identified.

11.1.4 KEY ROLES AND STUDY GOVERNANCE

Trial Chief Investigator:
Dr Adelina Pellicer PhD
Chair of Dept. of Neonatology
La Paz University Hospital (HULP)
Madrid, Spain

Central Clinical Data Management and Biostatistics:
Manuel García Goñi
Depertment of Applied & Structural Economics and History
Faculty of Economics and Business
Campus de Somosaguas, UCM
Madrid, Spain

Central Clinical Trial Management:
SERMAS-FIBHULP & Hospital La Paz Institute for Health Research (IdiPAZ)
Central Research and Clinical Trials Unit at La Paz University Hospital (UCICEC-HULP)
Madrid, Spain
www.idipaz.es

National Coordination
Each participating country will assign a **National Coordinator** who will provide a solution for all required trial management, and monitoring management at a national level.

11.1.5 ETHICS ADVISORY BOARD

11.1.6 CLINICAL MONITORING

The trial will be monitored according to the ICH GCP guidelines, and a detailed Clinical Monitoring Plan (CMP) will be developed by the Sponsor (SERMAS-FIBHULP) to assure the quality of the trial and that each person involved in the monitoring process carries out their duties. The CMP describes in detail who will conduct the monitoring, the frequency and level of detail of monitoring to be performed, and the distribution of monitoring reports.

Site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements. National Coordinators will be responsible for the provision of monitors in each country. Monitoring activities include

communication with the clinical investigator and study site staff; review of the study site process, procedures and records, and verification of the accuracy of data submitted to the sponsor.

Independent audits will be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP. Central daily check of recruitment to the trial, and the quality, completeness, as well as the timeliness of the entry of data in the eCRF by the data manager will be accomplished. Statistics of the internal monitoring will be published on the trial website.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The sponsor or designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Quality control procedures will be implemented beginning with the paper based primary study documentation that will be entered into the electronic data entry system by generating data quality control checks on the database (edit checks). Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Training for the study will be provided at the Study investigator's meeting (if applicable) and for site personnel prior to the initiation of study

Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Serious Breaches

A serious breach is defined as “A breach of GCP if applicable or the study protocol which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or
(b) The scientific value of the study.

In the event that a serious breach is suspected the Sponsor or designated organization should be contacted as soon as possible.

Any serious breaches will be notified to the competent Regulatory Authority according to applicable legislation.

Study file

The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents. It is recommended that the Investigator retain the study documents at least twenty-five years after the completion or discontinuation of the Clinical Trial. However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents within the fifteen year period following the Clinical Trial completion or discontinuation.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Source Document

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable to use paper based CRFs as source document in this study, all information required for the trial needs to be documented in the patient records of the hospital and transferred to the study eCRF.

Direct Access to Source Data/Documents

Direct access to source data will be granted to authorize representatives from the Sponsor or delegated organization, host institution, Ethic Committees and Regulatory Authorities study-related for monitoring, audits and inspections.

The investigator should inform the Sponsor as soon as he gets knowledge of an inspection.

In case of any finding during an audit or inspection the Sponsor and investigators will apply the corresponding corrective actions.

Study Data Collection

eCRFs has been designed in collaboration between SERMAS-FIBHULP to register every item of data required in the protocol and recorded by the investigator. eCRFs will be completed per patient under respect of the data protection law for every country and will then be transferred into the eCRF-system.

SERMAS-FIBHULP have designed, tested, implemented, and is maintaining an electronic data entry system and database through a suitable web interface in a timely manner. Design and implementation of eCRFs require a data dictionary set up in consensus with the Sponsor and signed by statistician, principal investigator and Sponsor.

There will be several possible time points for data entry: screening, enrolment, weekly visit up to discharge to home or transfer to a non-FICare centre, short-term clinical outcome assessment, mid-term clinical outcome assessment and long-term clinical outcome assessment. If the infant in the meantime has been discharged to a step-down unit, data should be sought from the specific unit. If this is not possible, data should be used until the date of discharge to step-down unit. Data will be stored in accordance with guidelines issued by the Spanish Data Protection Agency.

The electronic data entry system provides an audit trail, allowing identified and authorised users to remotely store data in the eCRFs so that all data entries and changes done by sites in the central database are automatically and chronologically recorded.

The monitor should ensure that the eCRFs are fully and correctly completed according to the source documents. Investigator will assure that all data recorded in the eCRF correspond with the information recorded in the source documents.

All source data used to complete electronic forms will be stored and archived at each investigation site.

Data Management

FIBHULP will be responsible for the data management and storage of the study data (on a database) including:

Data storage and backup: The study server running the database is regularly maintained by the manufacturer. Twice a day a backup of the database with pseudonymised study data and the application data is automatically generated. Further storage of the dump files at an additional secure area and protected by a password will be issued. These backups can be used to restore the data and the application for electronic data capture on another server within a short time-period.

Data validation: Data will be validated according to the data validation plan.

Data coding: medical history, adverse events (when applicable please refer to the assessment of safety section of the protocol) and any abnormality obtained on any study test result will be coded using MedDRA and concomitant treatments using WHO-DD. Codification procedure is described on a specific manual.

After conducting all data validation and the final review, the study database will be considered as completed and its containing data as reliable. At this moment, the study database will be closed and transferred to the Biostatisticians team for data analyses.

At the end of the study a copy of the site-specific records will be provided to each principal investigator.

11.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.1.9 PUBLICATION AND DATA SHARING POLICY

It is paramount for RISEinFAMILY to maximise outputs and foster external exposure from all partners, but without jeopardising scientific integrity or compromising major scientific papers. To help achieve this, the present document describes the set of rules and procedures in place to ensure a uniform standard and quality of RISEinFAMILY publications. The policy also intends to avoid effort duplication and guarantee the legal protection of Copyright to RISEinFAMILY work.

Publications refer to material used to make RISEinFAMILY information public and disseminate all results and findings. Publications can be of two types:

- Scientific publications are those documents submitted to a professional journal listed in the Index Medicus or to a scientific meeting as an abstract. All manuscripts resulting from RISEinFAMILY should be published in peer reviewed journals. All conference abstracts must be generated with a commitment to subsequent manuscript publication.
- Non-scientific publications are those materials, other than scientific journal publications and scientific conference presentations, used to support RISEinFAMILY dissemination activities. This includes teaching materials (documents, videos…) workshops, websites and web-applications, press releases, flyers, posters, videos, media briefings, articles in popular press, presentations, exhibitions, media appearances (radio, TV), interviews, etc.

Clinical Publication Committee (CPC)

The CPC shall deal with all aspects regarding publications that arise from RISEinFAMILY activities.

Members of this Committee shall be:

Publication Approval

Partners interested in producing RISEinFAMILY publications shall submit a 1–2-page proposal to the CPC for approval

Only authors who complete the publication approval process described above can submit an abstract for conferences, begin data analyses and submit a manuscript to journals.

Data Management for Scientific Publications

FIBHULP will guard the research data through a web-based electronic clinical trials data management system.

All multicentre data analysis shall be conducted together with FIBHULP. At least one partner from SERMAS and FIBHULP should be author on every publication from RISEinFAMILY multicentre clinical data.

For single site data analysis: All RISEinFAMILY site investigators will receive, upon request to FIBHULP, a file of all data on all subjects enrolled at their institutions in the RISEinFAMILY project after database closure and finalising of the clinical trial report. FIBHULP will not in all instances be able to provide data analysis for single institution publications, though it will be happy to provide advice and guidance. Publication and presentation, including rules of authorship and acknowledgement, for such publications will be determined by the site investigator and their institution, except that the universal RISEinFAMILY acknowledgements policy must be adhered to, and that prior approval for analysis must be sought from the CPC to ensure no conflict with ongoing or planned analyses of the same topic in the entire database.

Any publication based on the results obtained at a single trial site (or a group of trial sites) shall not be made before the first multicentre publication(s). The publication shall make reference to the relevant multicentre publication(s).

Publication Approval Timings

In order to ensure that the CPC will be able to make comments and suggestions where pertinent, the publication proposal form should be submitted to the CPC for review at least twenty (20) days prior to submission for publication, public dissemination, or review by a publication/conference committee.

During the period of review of a proposed publication, the CPC will consult the sponsor of the study and all RISEinFAMILY partners, by giving at least 10 days prior notice of any intended publication.

Following notification, any of those beneficiaries may object within 5 days of the notification to the envisaged dissemination activity if it considers that its legitimate interests could suffer disproportionately great harm. In such cases, the dissemination activity may not take place or may be delayed until appropriate steps are taken to safeguard these legitimate interests, like protecting proprietary information and/or Intellectual Property Rights and Know How.

Proper Identification of RISEinFAMILY Origin and Funding

All publications generated from RISEinFAMILY clinical data shall be published by individual authors and co-authors “on behalf of the RISEinFAMILY Consortium”.

All PIs shall be listed in a list of contributors with each publication, entitled “RISEinFAMILY Consortium”. Such updated list shall be maintained at SERMAS-FIBHULP and be available on the RISEinFAMILY website for all for cut-and-paste into publications.

In all cases where journal policies permit, all investigators who contribute patients to RISEinFAMILY will be acknowledged.

All publications shall include the following statement: the research leading to these results has received funding from the H2020-MSCA-RISE-2020.

11.2 ABBREVIATIONS

AE	Adverse Event
AR	Adverse reaction
BPD	Bronchopulmonary dysplasia
BW	Body Weight
CI	Confidence Interval
CLUJ	
CMP	Clinical Monitoring Plan

CPC	Clinical Publication Committee
CUs	Cranial ultrasound
DOL	Day of life
EDC	Electronic Data Capture
EC	Ethics Committee
eCRF	Electronic Case Report Form
EAB	Ethics Advisory Board
EFCNI	European Foundation for the Care of Newborn Infants
EoI	End of Intervention
EPDS	Edimburg Postnatal Depression Scale
ES	Spain
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FIBHULP	Fundación para la Investigación Biomédica del Hospital Universitario La Paz (Biomedic Investigation Foundation of La Paz University Hospital)
FiCARE	Family integrated care
GA	Gestational Age
GCP	Good Clinical Practice
GU	Guzi University
HULP	La Paz University Hospital
ICD	Informed Consent Documen
ICH	International Conference on Harmonisation
ITT	Intention-To-Treat
IVH	Intraventricular haemorrhage
MedDRA	Medical Dictionary for Regulatory Activities
NICU	Neonatal Intensive Care Unit
NL	Netherland
OLVG	
OR	Odds Ratio
PI	Principal Investigator
PMA	postmenstrual age
PSS-NICU scale	Pediatric Stress Scale-NICU scale
ProQOL scale	Pro Quality of Life scale
RO	Romania
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SAR	Serious adverse reaction
SAE	Serious Adverse Event
SAR	Serious adverse drug reaction
SERMAS	Servicio Madrileño de Salud (Madrid, Spain)
SNAPPE-II	Score for Neonatal Acute Physiology Perinatal Extension
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
TR	Turkey
TSC	Trial Steering Committee

UCICEC	Central Research and Clinical Trials Unit
UCICEC-HULP	Central Research and Clinical Trials Unit at La Paz University Hospital
UK	United Kingdom
UM	University of Miami
UHS	University Hospitals Sussex
US	United States
ZM	Zambia midwivesassociation
ZSM	University of Zambia School of Medicine

12 REFERENCES

Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. Health Econ 2006;15:373-81 DOI:10.1002/hec.1068

Barnes CR, Adamson-Macedo EN. Perceived maternal parenting self-efficacy (PMP S-E) tool: Development and validation with mothers of hospitalized preterm neonates. J Adv Nurs 2007; 60:550-560 doi: 10.1111/j.1365-2648.2007.04445.x

Banerjee J, Aloysius A, Mitchell K, Silva I, Rallis D, Godambe SV, Deier A. Improving infant outcomes through implementation of a family integrated care bundle including a parent supporting mobile application. Arch. Dis. Child. Fetal Neonatal Ed. 2020;**105:** F172–F177 doi. org/ 10. 1136/ archdischild- 2018- 316435.

Baltussen, Rob M. P. M, Adam, Taghreed, Tan-Torres Edejer, Tessa, Hutubessy, Raymond C. W. et al. Making choices in health : WHO guide to cost-effectiveness analysis 2003. T. Tan-Torres Edejer ... [et al] Eds. World Health Organization. https://apps.who.int/iris/handle/10665/42699

Behrman RE, Butler AS Ed. Committee on Understanding Premature Birth and Assuring Healthy Outcomes (2010). Mortality and Acute Complications in Preterm Infants. [online] Nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK11385/.

Benzies KM, Shah V, Aziz K, Isaranuwatchai W, Palacio-Derflingher L, Scotland J, Larocque J. et al. Family Integrated Care (FICare) in Level II Neonatal Intensive Care Units: Study protocol for a cluster randomized controlled trial. Trials **18**, 1–12 (2017). DOI 10.1186/s13063-017-2181-3

Bhutta ZA, Khan I, Salat S, Raza F, Ara H. Reducing length of stay in hospital for very low birthweight infants by involving mothers in a stepdown unit:.an experience from Karachi (Pakistan) BMJ 2004;329: 1151–55. DOI 10.1136/bmj.329.7475.1151.

Blencowe, H., et al. (2012). National, regional and worldwide estimates of preterm birth rates in the year 2010: a systematic analysis. Lancet. 2012 Jun 9;379(9832):2162-72

Bouet KM, Claudio N, Ramirez V, Garcia-Fragoso L. Loss of parental role as a cause of stress in the neonatal intensive care unit. Bol Asoc Med P R 2012; 104: 8–11.

Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.

Brockington IF, Fraser C, Wilson D. The postpartum bonding questionnaire: a validation. Arch Womens Ment Health (2006) 9: 233–242 DOI 10.1007/s00737-006-0132-1

Church PT, Grunau RE, MIrea L, Petrie J, Soraisham AS, Synnes A, Ye XY, O'Brien K. Family Integrated Care (FICare): Positive impact on behavioural outcomes at 18 months. Early Hum. Dev. **151**, 105196 (2020) doi.org/10.1016/j.earlhumdev.2020.105196.

Cormack B, Embleton ND, van Goudoever JB, Hay WW, Bloomfield FH. Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. Pediatr Res 2016;79: 810–820 https://doi.org/10.1038/pr.2016.26

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item . Edinburgh Postnatal Depression Scale. British Journal of Psychiatry 1987;150:782-786 doi: 10.1192/bjp.150.6.782

Doherr H, Christalle E, Kriston L, Härter M, Scholl I. Use of the 9-item Shared Decision Making Questionnaire (SDM-Q-9 and SDM-Q-Doc) in intervention studies—a systematic review. PloS one 2017;12:e0173904 doi.org/10.1371/journal.pone.0173904.

Fenton 2013 Growth calculator for preterm infants-PediTools (htpps//:pedotools.org/fenton2013)

Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information:

combined and uneven development. Med Decis Making. 2008; 28(1):21-32 doi: 10.1177/0272989X07308751.

Hansen M, Andersen TE, Armour C, Elklit A, Palic S, Mackrill T. PTSD-8: a short PTSD inventory. Clinical practice and epidemiology in mental health 2010;6:101-108

He SW, Xiong YE, Zhu LH, Bo LV, Gao XR, Xiong H. et al. Impact of family integrated care on infants' clinical outcomes in two children's hospitals in China: A pre-post intervention study. Ital. J. Pediatr. **44**, 1–7 (2018) doi.org/10.1186/s13052-018-0506-9.

Hei M, Gao X, Li Y, Gao X, Li Z, Xia S, et al. Family Integrated Care for Preterm Infants in China:

A Cluster Randomized Controlled Trial. J. Pediatr. **228**, 36-43.e2 (2021) doi.org/10.1016/j.peds.2020.09.006.

Hoomans T, Ament AJ, Evers SM, Severens JL. Implementing guidelines into clinical practice: what

is the value? J Eval Clin Pract. 2011; 17(4):606-14 doi:10.1111/j.1365-2753.2010.01557.x.

Husereau D, Drummond M, Petrou S et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013;16:231-50 doi: 10.1016/j.jval.2013.02.002

Johnson S, Bountziouka V, Linsell L, Brocklehurst P, Marlow N, Wolke D, Manktelow B. Parent report of children's abilities-revised (PARKA-R). Technical and interpretive manual. University of Leicester, Leicester, 2019.

Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultrabrief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50:613-21.

Levey A, Glickstein JS, Kleinman CS, Levasseur SM, Chen J, Gersony WM, Williams IA. The Impact of Prenatal Diagnosis of Complex Congenital Heart Disease on Neonatal Outcomes. Pediatr Cardiol 2010;31:587–97 DOI 10.1007/s00246-010-9648-2.

Miles MS, Funk SG, Carlson J. Parental stressor scale: neonatal intensive care unit. Nurs Res. May-Jun 1993;42(3):148-52. PMID: 8506163

Moreno-Sanz B, Montes MT, Antón M, Serrada MT, Cabrera M, Pellicer A. Scaling up the family integrated care model in a level IIIC neonatal intensive care unit: a systematic approach to the methods and effort taken for implementation. Front. Pediatr. 9:682097 doi: 10.3389/fped.2021.682097

O'Brien K, Bracht M, Macdonell K, McBride T, Robson K, O'Leary L et al. A pilot cohort analytic study of Family Integrated Care in a Canadian neonatal intensive care unit. BMC Pregnancy Childbirth 20**13; 13(Suppl 1):** S12 http://www.biomedcentral.com/1471-2393/13/S1/S12.

O´Brian K, Robson K, Bracht M, Cruz M, Lui K, Alvaro R, et al. Effectiveness of Family Integrated Care in neonatal intensive care units on infant and parent outcomes: a multicenter, multinational, cluster-randomised controlled trial. Lancet Child Adolesc Health 2018;2: 245-254 dx.doi.org/10.1016/S2352-4642(18)30039-7

Ortenstrand A, Westrup B, Brostrom EB, Sarman I, Akerström S, Brune T, et al. The Stockholm Neonatal Family Centered Care study: effects on length of stay and infant morbidity. Pediatrics 2010; 125: e278–85 doi/10.1542/peds.2009-1511.

Palisano RJ, Cameron D, Rosenbaum PL, Walter SD, Russell D. Stability of the l Gross Motor Function Classification System. Dev Med Child Neurol 2006; 48:424-8 doi: 10.1017/S0012162206000934

Patel AL, Engstrom JL, Meier PP, Kimura RE. Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. Pediatrics 2005;116:1666-73 doi:10.1542/peds.2004-1699

Plomgaard AM, Hagman C, Alderliesten T, Austin T, vanBel F, Claris O, et al. Brain injury in the international multicenter randomized SafeBoosC phase II feasibility trial: cranial ultrasound and magnetic resonance imaging assessments. Pediatr Res 2016;79: 466-72 doi:10.1038/pr.2015.239

Ramsey SD, Willke RJ, Glick HA, et al. Cost-effectiveness analysis alongside clinical trials II: An ISPOR good research practices task force report. Value Health 2015;18:161-172 doi: 10.1016/j.jval.2015.02.001

Rochow N, Fusch G, Ali A, Bhatia A, So HY, Iskander R, et al. Individualized target fortification of breast milk with protein, carbohydrates, and fat for preterm infants: A double blind randomized controlled trial. Clin Nutr 2021;40:54-63 doi.org/10.1016/j.clnu.2020.04.031

Schaufeli WB, Leiter MP, Maslach C, Jackson SE (1996). The Maslach Burnout Inventory-General Survey. In Maslach C, Jackson SE, Leiter MP editors, Maslach Burnout Inventory 3rd Edition. Palo Alto: Consulting Psychologists Press, 19–26.

Schaufeli WB, Bakker AB (2003). Test manual for the Utrecht Work Engagement Scale. Unpublished manuscript, Utrecht University, the Netherlands. Retrieved from http://www.schaufeli.com Schaufeli, W. B., & Bakker, A. B. (2004).

Severens JL, Hoomans T. Economic evaluation of implementation strategies in health care. Implement Sci 2014;9:168. http://www.implementationscience.com/content/9/1/168

Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017;390:1770-80 doi.org/10.1016/ S0140-6736(17)31002-4

Smith BW, Tooley EM, Christopher PJ, Kay VS (2010). Resilience as the Ability to Bounce Back from Stress: A Neglected Personal Resource? The Journal of Positive Psychology 2010;5:166-176 doi.org/10.1080/17439760.2010.482186

Synnes AR, Petrie J, Grunau RE, Church P, Kelly E, Moddemann D, et al. Family integrated care: very preterm neurodevelopmental outcomes at 18 months. Arch. Dis. Child. Fetal Neonatal Ed. 2022;107:F76-F81 doi:10.1136/archdischild-2020-321055.

Spielberger CD, Gorsuch RL, Lushene TE, Vagg PR, Jacobs GA (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.(Spanish adaptation: Cuestionario de Ansiedad Estado-Rasgo (4thed.). Madrid: TEA, 1994)

Tich SN, Anderson PJ, Hunt RW, Lee KJ, Doyle LW, Inder TE. Neurodevelopmental and perinatal correlates of simple brain metrics in very preterm infants. Arch Pediatr Adolesc Med 2011; 165: 216–22

Walker S, Dixon S, Palmer S, Sculpher M. (2013) Getting cost-effectiveness technologies into practice: the value of implementation. Available at http://www.eepru.org.uk/wp-content/uploads/2018/09/eepru-report-getting-cost-effectiveness-dec-2013-014.pdf

van Veenendaal NR, van der Schoor SR, Heideman WH, Rijnhart JJ, Heymans MW, Twik JW, et al. Family integrated care in single family rooms for preterm infants and late-onset sepsis: a retrospective study and mediation analysis. Pediatr Res 2020;88:593-600 doi:10.1038/s41390-020-0875-9.

Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices-Modeling Studies. Value Health 2003;6:9-17 doi: 10.1046/j.1524-4733.2003.00234.x

WHO/EIP/KMS/2006.2 Bridging the 'know-do´ gap. Meeting on knowledge translation in Global Health.

Woodward LJ, Bora S, Clark CAC, Montgomery-Hönger A, Pritchard VE, Spencer C, Austin NC. Very preterm birth: maternal experiences of the neonatal intensive care environment. J Perinatol 2014; 34: 555–61 doi:10.1038/jp.2014.43.