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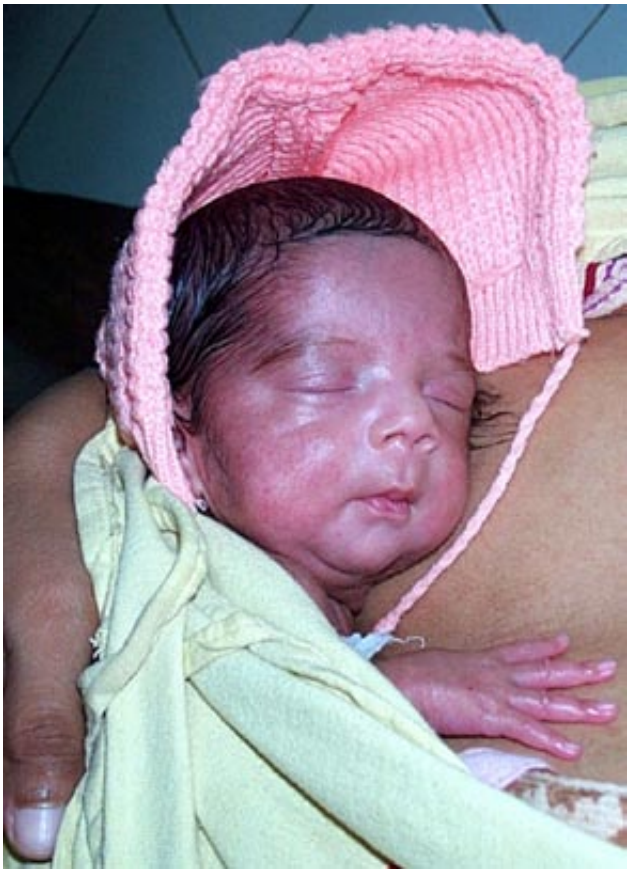
CLINICAL PRACTICAL GUIDELINES

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS AT BIRTH



Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine – Pontificia Universidad Javeriana
Bogotá, 2005 – 2007

Kangaroo Foundation

Coordination

Juan Gabriel Ruiz P[1], Nathalie Charpak[2]

Technical Staff:

Denis Granados[3] , Margarita Restrepo[4], María Cristina Torres[5].

Team

Carlos Alberto Calvache[6] (Kangaroo Dad), Alejandro Colmenares[7], Marta Cristo[8], María Claudia Duque Páramo[9], Zita Figueroa[10], Claudia González[11], Gabriel Longgi[12], Rosario Martínez[13], Rodrigo Pantoja Chaux[14], Lida Pinzón[15], Gloria Torres[16] (Kangaroo Mum), Viviana Rodríguez Torres[17], Lyda Rosero MD[18].

Sponsorship
Integral Kangaroo Mother Program, Bogotá, Colombia

1 MD MMedSci, Pediatrician, MA in Clinical Epidemiology, Head Professor, Department of Clinical Epidemiology and Biostatistics, Pediatrics Department, School of Medicine, Pontificia Universidad Javeriana
2 MD, Pediatrician, Fundación Canguro Director, Scientific Coordinator PMCI, Professor ad Honorem, Pediatrics Departa ment, School of Medicine, Pontificia Universidad Javeriana
3 MD, Research Assistant, Pontificia Universidad Javeriana
4 MD, Research Assistant, Pontificia Universidad Javeriana
5 Psi, Research Assistant, Pontificia Universidad Javeriana
6 Kangaroo Dad
7 MD, Pediatrician, specializing in Neonatology, Magister in Clinical Epidemiology Candidate, Instructor, Pediatrics Department, School of Medicine, Pontificia Universidad Javeriana. Neonatologist, Newborn Care Unit, Hospital Univer sitario San Ignacio
8 Psi, MSci, Psychologist, Magister in Clinical Psychology, Integral Kangaroo Mother Program, Fundación Canguro
9 PhD, Nurse, Specialist in Pediatrics Nursing, Magister in Community Psychology, PhD in Anthropology, Head Profe- ssor, School of Nurses, Pontificia Universidad Javeriana
10 MD, Pediatrician, subspecialist in Neonatology. PMCI Care Coordinator, Professor ad Honorem, Pediatrics Department, School of Medicine, Pontificia Universidad Javeriana
11 MD, Pediatrician, Saludcoop Kangaroo Mother Program.
12 MD, Pediatrician, specializing in Neonatology, Associate Professor, Pediatrics Department, School of Medicine, Univer sidad Nacional de Colombia, Pediatrics and Neonatology Department Director, Marly Clinic
13 Nurse, Mental Health, Maternity and Neonates Coordinator, Reina Sofía Clinic
14 MD, Pediatrician, Coordinator, Saludcoop Kangaroo Mother Program.
15 MD, Pediatrician, Neonatal Unit Director at Instituto Materno Infantil.
16 Kangaroo Mum
17 MD, Pediatrician, specializing in Neonatology, Instituto de los Seguros Sociales, San Pedro Claver Clinic.
18 MD, Pediatrician. Coordinator, Kangaroo Mother Program, Instituto de los Seguros Sociales, Clínica del Niño.

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- Adriano Cattaneo MD PhD, Unit for Health Services Research and International Health, IRCCS Burlo Garofolo, Via dell'Istria 65/1, 34137 Trieste, Italy
- Angela Huertas MD MSc FRCPCH, Consultant Neonatologist with special interest in neurodevelopment, Elizabeth Garret Anderson Hospital, University College London Hospital, Huntley Street, London WC1E 6DH
- Carmen R. Pallás Alonso, MD, Neonatologist, Jefe Departamento de Neonatología Hospital Universitario "12 de Octubre", Madrid, Spain

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General Content:

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS AT BIRTH

INTRODUCTION, THEORETICAL FRAMEWORK AND METHODOLOGY

Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine – Pontificia Universidad Javeriana
Bogotá, 2005 - 2007

Content:

Introduction

Outline

Clinical practice guidelines have been defined as "Systematically developed recommendations to assist physicians and patients in making decisions about appropriate health care for specific clinical circumstances" (JAMA 1995;274:570-4), or similarly as "Systematically developed statements to assist clinicians and patients in making appropriate health care choices for specific clinical circumstances" (Arch Intern Med 1990; 1811-8).

The evidence based recommendation is the structural and functional unit on which evidence based clinical practice guidelines are developed. In order to generate a specific recommendation, a specific point is first identified in the natural history or clinical course of a disease about which the clinician and the patient should make a decision (for example, choose among different diagnostic strategies); identifying all the alternative courses of action; searching and retrieving relevant scientific data, which are then critically appraised and summarized (evidence); stating a standardized judgment about their validity and relevance (evidence level); and issuing a graded recommendation on the most appropriate course to follow, based on the degree of confidence that it deserves.

Overall, there are three main categories of clinical practice guidelines according to the type of condition on which recommendations are made (SIGN 50: A guideline developers handbook) a) Focused on a condition or illness (e.g. Bronchopulmonary Dysplasia), b) Focused on a specific population (e.g. Preterm and/or low birthweight infants) and c) Focused on a particular technology or intervention (e.g. Kangaroo Mother Method). In the case of the first two categories, the definition for evidence-based recommendations and guidelines is consistent with the usual processes and specific developments for these types of guidelines (i.e., those that make recommendations about specific conditions or populations). Additionally, most of the published evidence based guidelines correspond to one of these first two categories. On the contrary, guidelines on the use of interventions or methodologies (the third category) differ significantly in terms of conception and development, and the definition of clinical practice guidelines per se (specific recommendations to aid doctor and patient in the decision-making process regarding clinical care under special circumstances) does not completely meet the content of this type of guidelines.

Typically, an evidence based recommendation provides both the practitioner and the patient with advise about what the best alternative is among the different potential courses of action to be chosen, thank to the fact that the expected usefulness is greater (risk-cost/benefit ratio) and that there is valid empirical evidence supporting this recommendation. In fact, recommendations are graded according to the strength of supporting evidence (level of evidence) and the benefit that these recommendations are expected to produce in a defined population (input to formulate the degree of recommendation). For example, in the case of a preterm baby unable to regulate temperature and for whom it is necessary to provide a neutral thermal environment, different approaches to this problem are analyzed (closed incubator, open radiant incubator, radiant heat warmed cot, cot with covers, kangaroo position, etc.), evidence that compares effectiveness, safety and costs of the different alternatives is collected and reviewed, and then a recommendation is made on the most appropriate alternative in some specific circumstances.

In the case of the formulation of practice guidelines about a method or intervention, the scenario is different. It is not a question of choosing among management alternatives, but of evaluating a specific management alternative (that one formulated by the intervention or technology of interest), identifying rational and scientific bases, critically appraising them, describing if the expected effects or those attributed to the alternative have a sound scientific support and eventually describing how, in whom, with what objective, with what magnitude and duration, and by whom the evaluated management should be carried out. For instance, in the case of the kangaroo position in stable preterm infants, an accurate description is provided about what the intervention consists of, what the therapeutic objectives expected to be reached are (thermal regulation, strengthening of the mother-child bond, promotion of breastfeeding, etc.), what the potential risks and benefits are, what evidence there is in favor to one or the others, what the expected risk/benefit ratio is, what the appropriate indications, circumstances and warnings are on the use of the KP.

The US Agency for Healthcare Research and Quality (AHRQ) considers 11 guideline categories by their main

focus, all of which consist of recommendations to manage conditions or illnesses, or populational groups (the first two previously mentioned categories) and only one includes recommendations on the appropriate use of technologies and interventions.

Strategic Decisions

The challenge that we face as authors to develop a guideline about the optimal management of a complex intervention as the kangaroo mother method resulted in having to implement a certain degree of methodological innovation since we were not able to find any publications related to guidelines, protocols or systems on how to assemble and develop evidence based recommendations for the use of complex interventions. Recommendations to perform health technology assessment are partially applicable to our objective because the purpose of this assessment is to adequately report to those involved in health care policy decision-making, but its contents and recommendations are not necessarily relevant to support a physician or patient in providing optimal health care. The group devised and adopted the following strategy:

1. Conceptualization: the kangaroo mother intervention was clearly identified by accurately defining the population on which the intervention is focused, the healthcare providers involved and the specific definition of each component: kangaroo position, kangaroo feeding strategy, kangaroo discharge policies and follow-up.

2. Evidence-Based Answers:

    a. A list of questions was made about the expected effects and therapeutic targets in specific populations. Example: *Is there any evidence that a stable preterm infant who is still unable to regulate temperature by being kept in the kangaroo position continuously and for a long term will regulate body temperature at least as well as an infant staying in a closed incubator that is working properly ?*

    b. Based on each question, a systematic search and review of the scientific literature was performed and relevant evidence was identified and critically appraised so as to provide ***an evidence based reply*** where the formulated question is answered by using scientific arguments and systematically reviewed empirical evidence.

    c. The type and reliability of the evidence associated to each reply was described in a standardized fashion ("level of evidence") and the degree of guideline developers agreement was described for each reply ("consensus level").

    d. Finally, the rational basis, the theoretical constructs and the reviewed and analyzed research specific results were discussed as per each evidence based reply to support and explain the evidence based reply reached by the group.

3. Recommendations: At the end of the description of the critical appraisal of the replies related to each of the relevant questions for each one of the three components evaluated in the kangaroo intervention (kangaroo position, feeding strategy and, discharge and follow-up policies) the specific steps and methods were listed as management protocols and as per the implementation of each component. For developing these recommendations, the experience and management protocols currently employedf by the different groups who participated in the elaboration of the current guidelines, (with ample experience in kangaroo mother care) were used as the core material for developing the recommendations. These pieces of material were reviewed in the light of the *evidence based replies*, and amended and corrected when necessary.

Rationale

Why Develop Clinical Practice Guidelines about the Kangaroo Mother Intervention

Burden of Disease: The extent of the adequate care requirement for the preterm and/or low birthweight newborn is increasingly high; the world distribution map of low birthweight infants overlaps the poverty map, in Colombia and worldwide. The impact, cost and rationality of prematurity and low birthweight prevention alternatives

and the subsequent management of these preterm and low birthweight infants are not obvious. The demand of healthcare services is always higher than available resources, even in better-off societies. Resources are not only finite but their use in a determined problem prevents its use to solve other problems. The cost of missed opportunity when using resources with a determined aim should lead to careful, rational and even choices at the time of using alternative interventions to tackle the same problem. Overall, the inappropriate use of resources shrinks the possibility of a more comprehensive and better quality care.

Variability of the Clinical Practice: In the current health care scenario in Colombia, the number of available therapeutic alternatives to offer patients who can take advantage of the kangaroo mother intervention is limited to two large pathways: Hospitalization with neutral thermal environment management until reaching maturity and/ or pre-established weight levels, or initiating and maintaining the kangaroo mother intervention (in hospital, and eventually ambulatory). However, both the clinician in charge of this type of patients as well as the infant´s parents do not always have clear, timely, and scientifically sound information that will enable them to make a free and rational decision on the use of the kangaroo mother method. Additionally, there is a lot of variability in the scientific literature and in the neonatology practice regarding what the method consists of, what its components are, how to adequately use them and if it is necessary to perform a rational standardization process to clearly distinguish what the practical aspects under the term "kangaroo mother intervention" are, whether they are scientifically sound, if they enable to really reach the objectives they state they meet and provide an adequate benefit/risk ratio.

Opposite to the need of scientifically supported standardization, what is observed is a practice variability for the management of the preterm and/or low birthweight newborn that cannot always be rationally accounted for. Sometimes the effectiveness of different approaches to face several problems is not supported by the scientific evidence or specific reasons (for example: existing resources, cost-effectiveness) but they seem to obey to the lack of clarity of clinicians, health care managers, and scientific directors working for health care promoting organizations, about the usefulness and safety of the different available management alternatives. There are programs for the early discharge from neonatal units, with very different kinds of management, length, supervision and cointerventions which are claimed to be kangaroo mother interventions.

Need of Clinicians´ Adequate Update: In the current clinical practice it is expected that a healthcare provider is able not only to perform as a content expert but also to critically and efficiently appraise the latest scientific evidence that is being produced on a continuous basis. The extent of this effort can go beyond time and resources availability of most of clinicians who are willing to keep updated. To critically and rationally digest the latest evidence is a very difficult demand to meet, but clinicians should try to accomplish it to offer the best possible care to patients.

The development of clinical practice guidelines is an adequate and efficient response to the formerly described situation. If recommendations made in guidelines are adequate and valid, healthcare providers compliance to them will enable to improve the consistency and quality of the care provided, enhance the rational use of resources and contribute to reducing the gap between knowledge production and its implementation in the clinical practice.

Why Develop Evidence Based Guidelines?
Recommendations included in a clinical practice guideline can be formulated following different methodologies. A relatively common alternative consists in gathering a group of experts chosen according to non uniform criteria and many times not even explicit, who will informally reach consensus. Some members of the group thank to their prestige or fervor end up imposing their opinions. In an effort to have a more even process, consensus development conferences, which became popular, thank to the National Institutes of Health (NIH) of the US, were created. In these conferences, systematic methods are followed to reach participants consensus. In this way the group's conscious or unconscious risk of manipulation decreases and contributions from all participants are evenly collected. The process is explicit and in theory, it is reproducible. However, to reach a consensus does not mean that recommendations are valid, it simply means that experts in a way are in agreement among themselves to formulate them.

In response to this problem the evidence based clinical practice guidelines were developed. In this case, experts in medical-technical contents and experts in evidence validity evaluate the corresponding information and, based on explicit, systematic and reproducible judgements regarding validity and relevance of the reviewed pieces of evidence, they formulate their recommendations.

Although there is scarce empirical evidence evaluating the superiority of one or the other method for the development of guidelines, a significant proportion of academic, government and hospital institutions, and of clinicians is in favor of evidence based guidelines. The main reasons that make evidence based guidelines favorite are:

a) It is an explicit, systematic and reproducible process.

b) It depends on the systematic and up to a certain extent more objective evaluation of pieces of evidence, instead of being founded on experts´ opinions (based or not on scientific pieces of evidence).

c) The evidence stemming from multiple well conducted investigations, with congruent results is more likely to lead to valid recommendations than the experts' clinical observations (non controlled) which are more prone to systematic sources of error (biases) and to random variability (i.e. regression to the mean).

d) There is evidence which indicates that when clinicians believe that recommendations are evidence based this fact increases their acceptance and use.

Why should University Departments get involved in their development and why the Kangaroo Foundation, in the specific case of the Kangaroo Mother Method?

University departments are academic units devoted to the culture, development, teaching and utilization of specific sciences and disciplines. Health science departments and in particular those devoted to clinical disciplines, develop most of the teaching, research and service activities (these are the functions that characterize the University) through the clinical units in health university institutions. Teachers and researchers that work in the duly accredited University Departments carry out an academic career and their activity is subjected to rigurous standards of quality and ethics, supervised by university authorities. In principle, among these professors and students (especially postgraduate students) there are technically trained and qualified personnel who are not closely tied to business compromises that might give rise to conflicts of interest which might distort the objectivity of recommendations included in the guidelines.

It is also the duty of universities to foster and apply socially useful knowledge. It is more likely that the clinical practice guidelines developed in academic settings reflect society priorities, values and needs, instead of reflecting only aims and interests of specific groups like healthcare providers or insurers.

Within the same spirit, the academic setting related to the direct delivery of services (as it occurs in clinical departments of university hospitals or in the specific case of the Kangaroo Foundation that provides health care, and carries out teaching and research activities in association with different university and school of health sciences clinical departments), should generate, evaluate and implement methodologies that ensure the quality of healthcare delivery. The quality thus sought is more likely to meet the requirements related to the true efficiency (adequate use of resources to obtain favorable health outcomes) and not merely productivity (number of service units generated by unit of resource, regardless of the quality of each unit of service, or generated *product*).

Finally, universities as social players have the duty to produce truthful and useful knowledge and ensure that its use responds to social interests (the best asset for the largest number of people) and are responsible to society which controls through different means the suitability of its performance.

The Fundación Canguro (with the support of the Department of Clinical Epidemiology and Biostatistics of the School of Medicine of the Universidad Javeriana) convened, set up and coordinated the team work of those individuals who developed the present guidelines. This group (as described below) tried to include the different players related to the development and use of the present guidelines by having a balanced and comprehensive composition.

Purposes and Objectives

Purposes of the Project

The purposes of the present project are:

1. To improve the healthcare quality and rational use of resources in the clinical management of preterm and/or low birthweight infants who are taken care of with the Kangaroo Mother Method.

2. To decrease the unjustifiable or inadequate variability in the implementation of the Kangaroo Mother Method primarily in Bogotá.

3. To help consolidate a culture of evidence based health policy making and rational clinical practice, susceptible to be audited, evaluated and improved.

4. To generate models of evaluation of research results (integrative research: clinical practice guidelines) that would pragmatically enable to measure and interpret simple, valid and useful impact indicators that will set the basis for evidence based healthcare quality assurance of the health care provided to target conditions.

Objectives

Overall Objective: The present project seeks to systematically and objectively develop a clinical practice guideline with its respective protocols and healthcare practice parameters for the Kangaroo Mother Method, based on the best and most updated available evidence. With the questions the clinician asks in each step of the healthcare process of a child subjected to the kangaroo mother method the aim is to elaborate evidence based responses ranked according to the level of evidence and degree of recommendation that are not only useful as a basis to guide the clinical practice but also that can be used to design, develop and carry out healthcare quality assurance activities.

Specific Objectives:

1. To perform a methodological and content diagnosis of preexisting kangaroo management guidelines.

2. To set up a task force integrated by representatives of the different players of interest: Guidelines "Client" (Ministry of Social Protection, District Secretariat of Health), Users (healthcare personnel from different preterm infants healthcare programs that use or might use the Kangaroo Mother Method), target population (preterm infants parents who have used the Kangaroo Mother Method), Academy (methodology and content experts), and other relevant players (Insurance Companies, Healthcare Promoting Agencies–EPS-, Health Promoters–IPS-, Scientific) for the development of the guideline.

3. To develop, adopt or adapt groups of evidence based recommendations (Clinical Practice Guidelines) that have at least the following components:

    a. Internal Validity: Evaluation of the efficacy, effectiveness and efficiency in each recommendation (level of evidence).

        i. Design of the Studies

        ii. Quality of the Conduction and Analysis

        iii. Evidence Consistency (among studies)

    b. Local Applicability: Degree in which populations and healthcare systems evaluated in the consulted studies match users and the target population of the guideline.

    c. Evaluation of how appropriate and relevant recommendations are locally and what is their impact on equity.

        i. Feasibility

        ii. Acceptability

        iii. Legality

    d. Degree of each recommendation

        i. Reliability of developers in recommended interventions risk/cost and benefits ratio.

ii. Evidence Level: Design of the studies + Quality of the conduction and analysis + Consistency of evidence.

iii. Relevance of Evidence (local applicability): Closeness to the study´s objectives regarding the question about the Guidelines, clinical relevance of reported outcomes, applicability to wider scenarios.

iv. Strength of the Evidence: Size, precision and consistency of reported effects (treatment), association (risk or prognostic factor) or discrimination capacity (diagnostic tests).

v. Patients' possibility to have access to interventions.

vi. Expected impact if recommendations were valid.

vii. Necessary Resources: Present and future economic feasibility.

4. To implement a process of external validation of guidelines through external peer evaluation and discussion in an ample but restricted forum (enlarged task force).

5. To elaborate a series of documents (tangible products):

   a. Final report about the development of guidelines with its results (recommendations).

      i. Recommendations

      ii. Clinical Management Protocols

      iii. References

      iv. Tables of Evidence

   b. Documentation of the process for the development of the guidelines.

Methodology

Design

It is an integrative researchproject aimed at developing evidence based recommendations. Each recommendation is the response to a scientific question related to the process of use of every one of the components of the Kangaroo Mother Method in a specific circumstance and in the quest of a determined therapeutic target. Questions formulated in terms of each of the items in the healthcare process where the guideline user and the patient have to make decisions on which step to follow. To generate a reply to each of the questions a systematic review of the scientific literature was carried out (data search, selection, retrieval and collection, critical appraisal and development of tables of evidence).

General Procedure

Methodological and Content Evaluation and Diagnosis of Existing Guidelines.

A search of guidelines specific to infants managed with the Kangaroo Mother Method was carried out. The group of methodological experts performed a critical appraisal of the guidelines by using the methodology and instruments proposed by the AGREE Collaboration(Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. www.agreecollaboration.org). The original instrument (translated into Spanish) is described in Appendix 1.

Development of the Guidelines

Guidelines were elaborated by using the following general methodology:

1. Explicit evaluation on the relevance of the specific topic

a. Significance of the chosen topic:

    i. Burden of Disease.

    ii. Differential Impact: It was studied whether mortality, severe morbidity and other significant outcomes were more frequent in some specific populational groups, particularly in communities and economically disadvantaged or vulnerable because of any other cause.

b. Wide and/or unexpected variability in the healthcare intervention decision making that makes difficult to understand if practices about which recommendations are made are presently rational, effective, cost/effective and reach fairly evenly all populational groups, even the most vulnerable ones.

c. Wide or unexpected variability of health outcomes, perhaps related to unwanted variability in the clinical practices.

d. Prevalent decisions and clinical practices not based on evidence but on other factors that might have a negative impact on the effectiveness of currently recommended interventions.

e. Potential to improve the healthcare quality with the formulation of specific evidence based recommendations:

    i. Possibility of improving healthcare outcomes.

    ii. Possibility of improving clinical decisions

    iii. Evidence of efficacious interventions: Effective and financially feasible interventions are available but are not widely used.

    iv. Possibility of rationalizing the use of resources.

    v. Special emphasis on diseases caused or worsened by inappropriate clinical practices: Iatrogenic diseases, adverse events, etc.

The topic was considered appropriate and the task force stated that it was necessary, desirable and feasible to develop the guidelines.

2. Purpose and Objectives Identification: The task force decided autonomously what the purposes and objectives should be. The following lines and concepts were used:

    a. Purpose:

        i. Normative (healthcare quality standards and/or practice parameters.

            1. Minimum Standards (conformity quality, minimum requeriments)

            2. Desirable Standards (Quality per requirements)

            3. Standards of Excellence (very high quality)

            4. Given that the group was not convened to develop standards, the purpose is not primarily normative. However, its use is proposed so that competent authorities are able to set up at least minimum and desirable standards on healthcare quality through the Kangaroo Mother Method.

        ii. Prescriptive (recommendations). The group defined the purpose of the guidelines primarily as recommendations (not mandatory, only supported by the scientific evidence authority) which should be met to standardize healthcare processes and improve its quality.

b. Objectives: The task force chose the objectives and decided not to focus on the management of prematurity and low birthweight but on the standardization of the Kangaroo Mother intervention. A systematic process that solved the following items was put in place:

i. Content: Main healthcare subject: Kangaroo Mother Method and all its components.

ii. The object of recommendations comprise the following domains:

1. Kangaroo Position: When to initiate it, continuity and duration, who is holding the baby, the effect of the skin-to-skin contact on temperature and physiological parameters, on the mother-child relationship, effect of the kangaroo position on the gastroesophageal reflux, primary apneas.

2. Strategy of the kangaroo feeding: what stage of extrauterine life adaptation, breastfeeding and other sources of nourishment, use of supplementation, nutritional objectives.

3. Discharge and follow-up policies

iii. Users: The task force decided to which healthcare professionals the recommendations are directed to and include: Pediatricians, neonatologists, general practitioners, professional nurses and nurse assistants.

iv. Target Population: To which infants and in which adaptation stages, to which families and with what objectives.

v. Scope: Primarily local, from Bogotá, although it is expected that they can be national and cover all the healthcare regiments in force in the country.

3. Contextualization of the Problem: The coordinating group provided documents to the task force for the contextualization. After members reviewed this documentation and contributed with their own input, several meetings were held to define:

a. Basic Information: Burden of disease, problems in which decisions are made, controversies, etc.

b. Construction of a model that represents a generic clinical scenario (called "typical" Kangaroo Method).

4. Explicit and systematic process of key questions identification, that used as a source the previously generated model (3. b) and whose responses are the scientific foundation of the specific recommendations. Two types of questions were asked: 1) Enumerative (what are the management alternatives in a situation, i.e. What are the nutrition sources employed in preterm newborns? 2) Comparative (What is the evidence that a specific component of the kangaroo method reaches an objective [thermal regulation] and how effective is it in comparison to the listed alternatives?) These last questions were the ones that guided the search strategy and were formulated by taking into account the following aspects:

a. Domain: Natural history and clinical course; physical examination; screening; diagnostic test; preventive, therapeutic, palliative or rehabilitation interventions, prognosis, quality of life and economic consequences of the disease and its management.

b. Population (inclusion and exclusion criteria)

c. Exposure (risk or prognostic factor, diagnostic or therapeutic intervention, etc.)

d. Control Exposure

e. Outcome:

i. Focused on the physiological disease or condition (morbidity, mortality, biological markers, physiological parameters, etc.)

1. Close
2. Distant

ii. Focused on the patient and family (close and distant).

1. Quality of Life
2. Satisfaction
3. Function (physical, psychological, social)

iii. Economic Outcomes (specifying the perspective)

To formulate questions the following general format was used: What is the evidence that in subjects…(population of interest, inclusion and exclusion criteria) exposed to… (exposure of interest) changes… (outcome of interest) as compared to similar subjects exposed to…(control exposure).

5. Identification of sources of evidence and systematic and comprehensive review of the evidence: the task force identified the sources of evidence to be consulted. These included: Index Medicus on Line (Medline, both PUBMED and MEDLINE OVID), National Guidelines Clearing House, Cochrane Library (OVID), Biblioteca Virtual en Salud (LILACS/BIREME, COL-OPS, MedCarib, PAHO, WHOLIS, Materna y Perinatal), HIRUNET, Dynamed (Ebsco Host), MedicLatina (EBSCO HOST), Nursing Journals (ProQuest), EBM Reviews (OVID) ISI Web of Science, Science Direct, Database of Abstracts of Reviews of Effectiveness (DARE) and TRIP Database,

a. Selection of papers and publications: For each question an explicit decision was made on:

i. Topic

ii. Design

iii. Inclusion and exclusion criteria

b. Search and Retrieval of Papers: Formulated standard strategies were used; they were developed by methodology experts by the Technical Team of the task force. The inventory of search filters developed by SIGN (see Annex 2) was also used. Mainly English and Spanish publications were used but depending on the specific relevance of some publications papers written in other languages were retrieved and translated.

c. Critical Appraisal

i. Standardized instruments of quality assessment methodology developed by SIGN (Appendix 3) were adapted.

1. Assessment of internal validity
2. Assessment of the quality of the design and study conduction
3. Determination of results consistency, clinical relevance and generalizability
4. Relevant information extraction

ii. Development of tables of evidence: Summary of all the validated evidence related to each key question.

iii. Assignment of levels of evidence to the evidence summary related to each key question: Design quality and adequacy, and quality evaluation. Robin Harbour and Juliet Miller´s (Harbour R,.Miller J. A new system for grading recommendations in evidence based guidelines) grading recommendations of evidence was used. *BMJ* 2001;**323**:334-6).

6. Formulation of evidence based responses with description of evidence levels and confidence in the assertion. The confidence in each assertion (equivalent to the degree of recommendation in a guideline for the management of diseases) was based on the following criteria:

    a. Confidence in the quality of the estimation made between the risk and cost balance, and the expected benefits.

    b. Evidence Level: Study design + quality of methods and conduction of studies.

    c. Evidence Relevance: Closeness to the study´s objectives regarding the question about the Guidelines, clinical relevance of reported outcomes, applicability to wider scenarios and patients.

    d. Evidence Strength: Effects size, precision and consistency from study to study (intervention), relationship (risk or prognostic factor), discriminative ability (diagnostic test) or economic consequences (cost/effectiveness, cost/usefulness or cost/benefit).

    e. Potential access of the target population to recommended interventions (economic, cultural, social and political barriers). Feasibility of the implementation and fair access to recommended interventions.

    f. Expected impact and local applicability (expected effect, i.e. Absolute risk reduction) if recommendations were valid.

    g. Resources Involved: Present and future economic feasibility, need to generate resources. "Second better" alternatives could be proposed based on the economic feasibility.

    h. To set up the levels of evidence the scale proposed by Harbour y Miller (SIGN) was used but instead of a semiquantitative grading, a list of the types of design and methodological quality was made.

    i. To describe the confidence in each evidence based response (equivalent to the degree of recommendation) Guyatt´s proposal (Guyatt G. Grading Recommendations - A Qualitative Approach) was taken into consideration. In Guyatt G, Rennie D, eds. *Users' Guides to the Medical Literature*, pp 599-688. Chicago: JAMA, 2002), also including apart from the remarks formerly described (6) the following considerations related to Local relevance and equity related aspects:

        i. Local Relevance:

            1. Local Applicability (generalizability)

                a. Aspects related to patients

                b. Aspects related to Users and/or Health Promoters (IPS)

                c. Cultural Aspects

            2. Feasibility: to have the necessary resources to carry out the recommendations with adequate levels or performance:

                a. Enough duly qualified human resources

                b. Technical resources (equipment, facilities, etc.)

                c. Financial resources (including sustainability)

                d. Administrative resources (appropriate and efficient allotment of

resources, management control, etc.)

e. Feasibility of the quality control, monitoring, assessment and adjustment.

3. Acceptability by all the players:

a. Clients: Political Support.

b. Users:

i. Apparent validity of recommendations

ii. Motivation and willingness to change practices.

iii. Conflicts of interest

iv. Hurdles to incorporate recommendations

1. Additional Workload

2. Perceived Administrative Support

3. Training

c. Target Population

i. Expectations met (perceived needs)

ii. Culturally appropriate recommendations

iii. Affordable (non medical direct costs, overheads)

iv. Preference by outcome (social values, quality of life)

ii. Equity:

1. Client's perspective:

a. Mandate

b. Cost/benefit

c. Opportunity cost of developing the recommendations

d. Geographic and populational differences in the distribution and burden of disease

e. Geographic and populational differences in the availability of resources

2. User's Perspective

a. Workload and remuneration.

b. Acknowledgement

c. Professional risks, including civil and criminal liability.

d. Geographic distribution of human resources

3. Target Population
    a. Applicability to special groups, minorities and vulnerable groups.
    b. Specific cultural problems in special groups
    c. Equal opportunity of access to interventions
    d. Social Support

7. Process of External Evaluation

The final draft of recommendations was subjected to a process of evaluation of its contents and face validity by third parties external to the process of formulation of recommendations , foreign peers experts in content and methodology (listed in the Acknowledgements).

STRATEGY

Functional Structure:
The main aim of the Coordinating Group is to assist members of the task force in the process of formulating appropriate recommendations, by helping them provide quality to this process in a given scenario. In this context "appropriate" means more than technically adequate, it also means to meet the needs and expectations of those affected by the formulated interventions.

The following functional structure was used for the development of the guidelines:

1. Task Force: the group of the guideline developers. It consists of 2 teams:
    a. Technical Team: An expert in content (that coordinates the task force) and a methodology expert (clinical epidemiologist). The first is staff who works for Fundación Canguro, the second is academic staff of the School of Medicine of the Pontificia Universidad Javeriana. Three research assistants with knowledge and expertise in systematic searches and critical appraisal took part.
    b. Work Team: Made up by representatives of the involved players, convened by consultants, with the support and backup of the Ministry of Social Protection. The players involved belong to the categories defined as follows:

The following categories of participants were defined

Clients are organizations involved in the decision making or in regulatory processes aimed at providing healthcare services (individually or collectively) in different levels: Policy makers (Ministry of Social Protection), Public or Private Healthcare Promoting Companies, Department or Municial Healthcare Authorities. What characterizes a client is that he or she has the capacity of modelling and/or regulating the decision making process for a specific healthcare area. The main clients appointed by the group are the Ministry of Social Protection of the Republic of Colombia and the District Secretariat of Health of Bogotá. They were invited to participate in the earliest stages of the set up of the task force.

Users are those who implement recommendations, what at an operative level implies to use the specific recommendations as an aid to make decisions. An example of a user would be the clinician, other healthcare providers and clients' decision makers. In the case of these guidelines, users are pediatricians, neonatologists working in private or public organizations and other healthcare providers who would perform specific actions to apply the Mother Kangaroo Technique in Public or Private Healthcare Services Companies (IPS) and/or at the level of the different kangaroo mother programs that are applying the kangaroo rules of the Ministry of Social Protection.

Target Population: Are those in whom formulated recommendations are applied. Mothers, fathers and families of preterm and low birthweight infants or organizations of the Civil Society acting as spokesperson are part of this category.

Academic Staff: Professionals expert in content and/or methodology with academic activity (university professors, researchers). This category includes experts that are part of the Technical Team, but it can convene other academic staff members that represent other disciplines involved.
Other players: Members of Scientific Associations, spokespersons of healthcare insurers (EPS) and medical and supplies technology providers. In the strategy we formulated, it is not forseen to include them directly in the task force but to involve them in the external validation phases (Virtual Forum, see below).

Specific Activities

Organization of the Task Force

The task force was set up by the voluntary participation of individuals who accepted the invitation to participate as representatives of different groups and organizations or as private experts.

Training

The Training Phase of the task force was carried out by teachers of the Department of Clinical Epidemiology and Biostatistics of the Universidad Javeriana. It covered two main aspects:

Consensus Methods

To allow that each member of the task force understands his or her role in the process of development of the guideline as well as that of the other members and to participate and accept the participation of others from the specificity of his or her role and field of expertise in an environment of respect and collaboration.

Standardization

To allow that all the members of the task force manage a common language both in the basic concepts of evidence based medicine as well as in the elaboration and use of the Clinical Practice Guidelines. The phase of standardization was developed in a workshop and covered the following aspects:

- Language and basic concepts of Evidence Based Medicine
- Introduction to the elaboration and use of the Evidence Based Clinical Practice Guidelines
- Group Dynamics and Consensus Generation Techniques

Development

In the phase of development 3 steps were carried out:

Conceptualization Phase

All the task force members participated (technical and work teams). It involved:

- Generation of the natural history-clinical course model and the identification of decision making items.
- Guideline related key questions

Evidence Search and Systematic Review Phase
It was primarily developed by the technical team with the collaboration of members of the task force to carry out specific tasks.

As described in the Methods Section, it implied to generate search strategies; inclusion and exclusion criteria; evidence search, screening and retrieval, critical appraisal for the assignment of levels of evidence and elaboration of evidence tables.

Phase of Generation and Preliminary Grading of Recommendations

All the task force members participated. In this phase recommendations were concluded by taking into account aspects described under Methods.
Recommendations also included an explanation of their lrationals, alternatives considered and for the grading phase

efficacy, effectiveness and efficiency aspects were taken into account as well as local and equity applicability.

Evaluation and Validation
This phase involves 2 independent processes.

External Peers Review and Evaluation

The final document was subjected to peers' review using the Support Group links to the "Internacional Network for Kangaroo Mother Care" (INK) and the "International Clinical Epidemiology Network" (INCLEN).

Users and Represented Organizations Review and Evaluation (legitimation)

Users' representatives in each task force will carry out an exercise of users' focal groups in their source institutions to know their opinions about the recommendations. Emphasis will be put in aspects related to Feasibility and Healthcare Personnel Acceptability This process is being implemented since the publication of the version corrected by external peers.

After the performance of these 2 processes, the members of the Task Force will evaluate the feeback obtained and will do the corresponding amendments to each of the recommendations. The final version of the recommendations and their grading will be settled by formal techniques of consensus generation.

Preparation of the Final Documents
Performed by the Technical Team together with the members of the Task Force.

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD

IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS

CONCEPTUALISATION

Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine – Pontificia Universidad Javeriana

Bogotá, 2005 - 2007

Contents

2. INTRODUCTION

2.1 Conceptualization of "Program", "Intervention" and "Method"

2.1.1 Term Variability

The terms "Kangaroo Care", "Kangaroo Management" or "Kangaroo Mother Program" have been used to refer to a number of interventions mainly targeted at preterm and/or low birthweight infants.

There is some heterogeneity in these interventions, resulting in the various terms with which they are identified: Kangaroo Care, Kangaroo Mother Care, Kangaroo Method, Kangaroo Mother Method, Kangaroo Mother Intervention, Kangaroo Technique, Kangaroo Program, Kangaroo Mother Program and skin-to-skin contact. Particularly the term "skin-to-skin contact" has often been used in the scientific literature in English to describe interventions using at least one of the main components of the Kangaroo Mother Care Method (KMCM).

2.1.2 Background to the "Kangaroo Mother Program"

The Program was initiated at the Instituto Materno Infantil (IMI) in Bogotá by Dr. Edgar Rey[19] in 1978. Coordinated by IMI's pediatricians Héctor Martínez and Luis Navarrete the program consolidated in its first 15 years and came to be known as "Kangaroo Mother Program". A group of investigators started the scientific assessment of IMI's Kangaroo Program in 1989, and in 1994 these researchers established the Kangaroo Foundation – an NGO in charge of evaluating, improving and disseminating the KMCM around the world.

The term Kangaroo Mother Program is based on specific meanings:

- **Program** implies it is based on a number of actions aimed at reducing mortality among preterm babies and making up for the lack of incubators;
- **Mother** means that mothers are requested to be actively involved in preterm infants' care;
- **Kangaroo** alludes to the extrauterine maturation of fetuses as it occurs in non-placental mammals, and implies that mothers continuously carry their preterm babies in the so-called Kangaroo Position (defined below).

2.1.1 Definitions for Method, Program and Intervention

The terms *program*, *intervention* and *method* are vaguely used in the scientific literature (and among health care professionals) resulting in some confusion. For the purposes of this guide the following definitions have been adopted:

- **The Kangaroo Mother Care Program** is the group of activities aimed at implementing a specific health care *intervention*; in this case the kangaroo mother intervention, with an adequately trained and organized health care team within a specific administrative and physical structure.
- **The intervention (Kangaroo Mother Care Intervention)** consists of a series of items that are applied thoroughly and systematically, following a certain method: the kangaroo mother care method.
- **The Kangaroo Mother Care Method** (KMCM) is a standardized and protocol-based care system for preterm and/or low birthweight infants, based on skin-to-skin contact between the preterm baby and the mother, which aims at empowering the mother (parents or caregivers) to gradually transfer the skills and responsibility to become the primary caregiver for their child, meeting each and every physical and emotional need.

2.1 Aims of the Guide

The purpose of this document is to describe, characterize and examine both scientific and empirical evidence of each of the components in KMCM. The aim is to identify and support with evidence all the key aspects involved in implementing the interventions on which the different components of the method are based.

This approach results in the development of specific recommendations concerning practices which have been validated as most effective in generating specific results (e.g. weight gain, thermal regulation). In addition, it helps define the indications for each recommended intervention and at the same time describe their benefits against other interventions.

19 Professor of Pediatrics at Universidad Nacional de Colombia

The present guides are not aimed at providing recommendations about design, planning, implementation, development and assessment of Kangaroo Mother Programs or to describe structural components defining the quality of a Kangaroo Mother Program.

The aim is to work out a method	The aim is not to assess a program
To identify the key aspects for each component involved in the kangaroo intervention; To describe, characterize and evaluate the rationale and the scientific evidence for each of the components of KMCM:	Quality of the program: The present guides do not seek to recommend design, planning, implementation, development or assessment of Kangaroo Mother Programs. Organizational quality: The main objective of this document is not to outline the structural components which define the quality of a Kangaroo Mother Program. To create specific quality indicators for each process in the kangaroo intervention and for therapeutic endpoints or targets.

3. FEATURES OF THE KANGAROO MOTHER METHOD

The Kangaroo Mother Intervention was conceived and implemented by the end of the 1970's at Instituto Materno Infantil (IMI) in Bogotá. From its beginnings, the method has been in constant evolution incorporating modifications based on practice and scientific research. The following statements about what the Kangaroo Mother Care Method (KMCM) consists of, basically reflects views on the evolution of concepts and processes held by "kangaroo" health care providers and researchers, and the rest of the participants involved in working teams elaborating these guides. It should be taken as the gold standard against which all evidence is assessed and variations of the Method derived from different settings and groups are contrasted.

To characterize and understand what the KMCM might consist of, it is necessary to outline some basic points: the population on which the intervention is focused, what the Kangaroo Position is, how kangaroo feeding and nutrition based on breastfeeding is conceived and which the kangaroo policies for hospital discharge and outpatient follow-up are.

Based on the description about these characteristic elements of KMCM, a "typical" or baseline, or reference scenario is outlined, which is useful to characterize elements and circumstances related to the implementation of KMCM. This scenario includes the elements that are basic to KMCM. Generating evidence-based statements is centered on identifying, retrieving, examining and summarizing the evidence regarding questions stemming from each of those basic elements. The description of this typical scenario is also useful as a checklist to avoid leaving aside any of the relevant aspects or elements related to providing the kangaroo mother care. Variations to this typical scenario are also described.

3.1 Target (Intervention) Population

The Kangaroo Mother Intervention is offered to preterm and/or low birthweight infants as soon as possible provided the baby can tolerate it: vital signs are stable, neither bradycardia nor hypoxemia is observed during manipulations, and there should be no primary apnea or, if previously present, it is already under control. Observational data from about 7000 "kangaroo" babies show that, when they reach a weight of 2500 g, about 95% of babies have already rejected the Kangaroo Position (Fundación Madre Canguro, unpublished data).

The kangaroo intervention does not replace neonatal care units, but it is a supplement to health care interventions on newborn infants.

Full term infants with adequate weight for their gestational age may profit from the Kangaroo Position for a limited period of time during the day and for a limited number of days (as long as they can tolerate and maintain the skin-to-skin contact), and there is evidence on the positive effect this position has in promoting breastfeeding and the mother-infant relationship. These effects are similar in terms of trend but not necessarily in magnitude to those

observed in preterm and/or low birthweight infants. Reviewing the evidence and the recommendations on the use of KMCM for healthy infants at term is beyond the scope of the present guide. Instead, it is focused on preterm babies or low birthweight full term infants.

3.2 Kangaroo Position

3.2.1 Reference Definition

The so-called Kangaroo Position is the hallmark of KMCM. Features for a "typical" or reference Kangaroo Position are:

- Mother to child skin-to-skin contact, 24 hours a day, placed vertically between the mother's breasts and below clothes. Mothers not only keep the infants' body temperature (fulfilling the function of incubators) but also they are the main source of nutrition and stimulation. A cloth (cotton or elastic synthetic fiber) elastic support is used to make the provider comfortable enough to relax and sleep while the infant is continuously maintained in the Kangaroo Position. The cloth support prevents the child's airway from obstructing after changes in position (e.g. neck flexion or hyperextension), and this is particularly important since positional obstructive apneas may result without this support given the preterm baby's usual hypotonic status.
- The baby may be fed at any time, held in the Kangaroo Position.
- Any other person (for example, the father) may share in the mother's role, holding the baby in the Kangaroo Position. A half-sitting position (30º) is to be adopted while sleeping.
- The Kangaroo Position should be maintained as long as the child tolerates it (babies will show they no longer accept the position because they start sweating, scratching and yelling or will clearly show discomfort every time their mothers hold them in the Kangaroo Position).

The objective of this position is that the baby finds in the mother a continuous source of body heat, kinetic and tactile stimulation, while patency of the airway is preserved. The position stimulates and favors breastfeeding. Additionally, close and sustained contact between mother and child allows to establish or reinforce a healthy biological and affective bond which should exist between all newborn infants and their mothers, and which may be hindered by the baby's prematurity and disease leading to a physical detachment of the mother and child. To this aim, the position should be: a) continuous, i.e. trying to keep interruptions to the minimum, b) sustained, i.e. most of the time, ideally 24-hourly and c) lasting as many days or weeks as the child needs it.

3.2.1 Variations of the Kangaroo Position

Variations to the Kangaroo Position, developed in different health institutions facing different problems, relate to three main aspects:

3.2.1.1 Time to Start:

Initiation of the Kangaroo Position has been described at different points as of birth, from immediate post-partum to hospital discharge as soon as the preterm baby is stable. Use of the Kangaroo Position as part of early stabilization maneuvers has also been described.

3.2.1.2 Continuity of the Position:

While some seek to maintain the position 24-hourly, others advocate an intermittent option for the baby on the mother's chest (alternatively using the incubator), for periods of minutes to a few hours. This intermittent modality is used especially for babies who are frail but stable, trying to reinforce the mother-child bond and breastfeeding.

3.2.1.3 Duration of the Intervention:

There are various schemes, for example during hospitalization only and then the baby is discharged out of the Kangaroo Position; others support maintaining the Kangaroo Position well beyond hospital discharge.

3.2.1.4 Identification of a Variation as KMCM

Regardless of initiation time, continuity and duration of the Kangaroo Position, all these alternatives may be identified as variations to the KMCM as long as they comply with the definition described above: holding the child in the Kangaroo Position. If the child is not held in the Kangaroo Position at a given time, the KMCM is definitely out of the question.

Other approximations involving parents who take care of their frail newborn babies and seek to humanize neonatology, for example, by changing the macro-environment but in which the child is not held in the Kangaroo Position (e.g. touch, carrying or breastfeeding the baby, NIDCAP[20], etc.) are out of the range of variations that may be identified as Kangaroo Mother Care Method.

3.3 Kangaroo Nutrition based on Breastfeeding

3.3.1 Introduction

Nutritional needs of low birthweight and preterm babies are heterogeneous. Firstly, newborn babies with the same low birthweight might be babies at full term with intrauterine malnutrition, preterm babies with an adequate weight and preterm babies with intrauterine growth restriction. Additionally, near term babies are included under the preterm category (e.g. 35-36 weeks), moderately preterm babies and very preterm babies (23-28 weeks' gestation at birth and weights lower than 1000 g). Their requirements and their ability to be fed may also change with certain concurrent conditions and diseases or transitional complications.

The baby's post-natal period is a very important factor in feeding and nutrition strategies for preterm, low birthweight and/or sick babies. Overall, three significant periods are described:

- *The transitional period*, from birth until the main aspects of immediate and mediate transition to extrauterine life are completed (usually from day 0 to day 10), where parenteral nutrition support and/or the use of strategies of adaptation of child's physiology to the use of the digestive tract for administering the nutritional requirements may be necessary.
- *The "steady growth" period*, where transition completes to reach full term, a period resembling the intrauterine growth which would have taken place had the baby been able to reach full term, in which the use of enteral feeding, particularly orally, is appropriate.
- *The "post-discharge period"*, as of full term (or hospital discharge 4-8 weeks after birth) until 1 year of corrected age.

3.3.1 Kangaroo Feeding and Nutrition Strategy (Reference)

The KMCM baby's feeding and nutrition strategy is based on the following:

3.3.1.1 Target Population:

The kangaroo feeding strategy is designed for babies in the so-called steady growth period. Feeding strategies in the transitional period (for example, parenteral nutrition) are not considered in this guide.

Similarly, and although they represent a way to continue with the feeding process started during the steady growth period, feeding strategies for babies in the post-discharge period are out of the scope of this guide.

3.3.1.2 Nutritional Source

Breastfeeding is the main nutritional source for the baby, and should be used whenever possible. Fat-soluble vitamins are always used to supplement breast milk. Breast milk may be fortified or supplemented whenever necessary. Donor breast milk may be an option, preferably of a similar gestational age, provided it is collected, pasteurized and given following safety precautions and its advantages and nutritional value are optimally preserved.

3.3.1.3 Feeding Route

Breastfeeding may occur via direct sucking on the breast or by expressed breast milk, which may be given orally or by gastroclysis, for example by intermittent *gavage*.

3.3.1.4 Clinical Goals

The aim of nutrition by breastfeeding is to take the most advantage of unaltered breast milk, particularly considering its immunological properties, the balanced intake of essential nutrients and its safety profile in terms of the risk of enterocolitis. The growth objective is a weight gain at least as significant as that of the intrauterine growth (15 g/Kg/day until term). Initially, breastfeeding is given at fixed intervals and not on demand, to ensure an appropriate, minimal intake.

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20 The kangaroo position has been recently incorporated as an important component in NIDCAP. In these cases, the intervention may be accepted as a variant within the interventions consistent with the Kangaroo Mother Care Method.

If the goal is not achieved with exclusive breastfeeding (supplemented by an intensive intervention -kangaroo adaptation-, including initiation strategies and implementation of breastfeeding), conditions that may explain inadequate weight gains should be investigated (e.g. anemia, infection, hypothermia, not compliance with the Kangaroo Position, etc.). Growth should improve once the underlying condition is managed. If the above still fails, or if no secondary causes for inadequate growth were found, breastfeeding should be supplemented either with fortification or with preterm formula, using a drip or spoon to avoid interfering with breastfeeding. Intake calculations should be based on the goal to supplement up to 30% of the recommended daily intake, and after at least 1 week's adequate growth a gradual reduction of supplementation is attempted; the ultimate aim is to attain exclusive breastfeeding at a 40-weeks post-conceptional age.

3.3.2 Variations: Kangaroo Mother Care Method and Breastfeeding

In some cases the Kangaroo Position becomes an option for babies who are not receiving the breastfeeding-based kangaroo nutrition strategy, such as those who still cannot suck or swallow, or who are receiving parenteral nutrition or nutrition by gastroclysis, or in those cases when breastfeeding is not possible (adopted child in kangaroo by the foster parents, mother's death, absolute or relative contraindications for breastfeeding). Although this component of KMCM cannot be administered, the care given to the child may still be considered a Kangaroo Mother Care Intervention if the Kangaroo Position is carefully followed.

3.4 Hospital Discharge and Outpatient Follow-up Policies

3.4.1 Objectives

The use of KMCM allows to gradually transferring the responsibilities for the baby's emotional and physical care from the health care staff to the baby's family, particularly the mother (and any other Kangaroo Position provider accepted by the family, e.g. the father, grandparents, etc.)

As continuous Kangaroo Position makes it possible to adequately regulate the baby's temperature and at the same time allows the permanent care and direct observation by the position provider, the baby's care is "demedicalized" earlier than in those cases where the baby is kept in an incubator or in a cot.

3.4.2 Reference Definition

3.4.2.1 Outline

Providing kangaroo care is a continuous process. Kangaroo Position and feeding are initiated at some time during hospitalization; this marks the beginning of the kangaroo adaptation, which is continued as long as the baby needs it, regardless of whether the child is in the hospital or not. In fact, after a successful adaptation of the mother and the baby to the Kangaroo Position and feeding, the hospital can offer very little which cannot be given to both in an appropriate outpatient setting. Therefore hospital kangaroo adaptation may be seen as a preparation for an appropriate, safe and successful discharge for both mother and child, and to enable home kangaroo care as long as required by the baby.

"Early" (timely) discharge in a Kangaroo Position is one of the components of the Kangaroo Mother Care Method. This early discharge, together with a close strict outpatient follow-up program, becomes a safe and effective alternative to permanence in the Neonatal Unit during the "steady growth" phase (outlined in 2.3.1). Though discharged, the baby continues to receive health care at least as comparable in terms of intensity and quality as that they would receive in a neonatal minimal care unit, is physically and emotionally integrated in the family, and at the same time nosocomial risks are prevented.

3.4.2.2 Timely Discharge in Kangaroo Position

Kangaroo babies become candidates to home kangaroo mother care as soon as the following is observed:

- A successful kangaroo adaptation (to the Kangaroo Position and feeding by both mother and child);
- The baby can suck, swallow and breathe synchronically[21].
- The family is willing and able to follow the protocols and the recommendations of the program and the follow-up policies strictly.
- Access to a systematic, rigorous, well-established program of outpatient care and kangaroo follow-up is available.

21 Certain Kangaroo Mother Programs have experience in referrals to outpatient management for babies receiving "gavage" (intermittent gastroclysis) feeding, administered by the appropriately trained mother (adequate suction or swallowing are not indispensable) or orally without suction (cup, spoon, drip; in this case the baby should swallow adequately).

Babies leave the hospital regardless of their weight or gestational age. Once at home, the babies are kept in a Kangaroo Position 24-hourly until they reject it.

3.4.2.1 Kangaroo Follow-up

After discharge, babies are controlled on a daily basis, monitoring weight until they get to a daily weight gain of 15 g/Kg/day. Subsequently, weekly controls are performed until they reach full term (40-week post-conceptional age and 2500 g). This is the outpatient equivalent of hospital minimal care and may be termed "outpatient neonatal minimal care". This includes systematic prophylactic treatments such as anti-reflux measures and drugs, vitamins, prophylaxis of the prematurity primary apnea, etc. Eye and neurological (including a brain ultrasound scan) screening tests are performed during this follow-up.

3.4.2.2 Follow-up of the High-risk Infant

This final phase of KMCM should be complemented with a high-risk newborn infant follow-up, at least until the baby reaches 1 year of corrected age. The rationale for this lies in the fact that kangaroo babies clearly belong to a category of high biological risk of inappropriate growth and presenting sensory and neuro-psychomotor developmental deficits. Although this is not directly addressed by this guide, a high-risk infant follow-up is essential after the kangaroo follow-up period per se is complete (40-week post-conceptional age or weight 2500 g, whatever happens later), and consequently the minimal activities a high-risk follow-up program should do are enumerated at the end.

3.4.3 Variations and Contrast with the Reference Definition

3.4.3.1 Destination after Discharge

On leaving the Neonatal Unit, the baby may be taken to a place inside the hospital or connected to it for mother-child kangaroo rooming-in (e.g. kangaroo ward), or directly to their homes.

3.4.3.2 Discharge Criteria

3.4.3.2.1 Discharge criterion for mother-child kangaroo rooming-in:

3.4.3.2.1.1 Regardless of weight or gestational age and as soon as both mother and child obtain a successful kangaroo adaptation (Kangaroo Position and feeding).

3.4.3.2.2 Discharge criteria for home kangaroo mother care:

3.4.3.2.2.1 Regardless of weight or gestational age and as soon as both mother and child obtain a successful kangaroo adaptation (Kangaroo Position and feeding);

3.4.3.2.2.2 The family is willing and able to follow the home KMCM protocols and follow-up policies strictly.

3.4.3.2.2.3 A Kangaroo Mother Care Program should guarantee close, timely outpatient follow-ups and be ready to provide emergency care for the baby under outpatient kangaroo mother care appropriately and whenever needed.

GLOSSARY

Prematurity: A state defined by a baby born before 37 weeks of gestation, regardless of weight.

Low Birthweight: A birthweight lower than 2500g regardless of gestational age.

Gestational Age at Birth: Duration of gestation estimated by means of obstetric methods (date of last menstrual period, ultrasound assessment of implantation, etc.) or pediatric scales assessing appearance and maturity of the baby in the first 72 hours of life: Amiel-Tison, Ballard and new Ballard, Capurro, Dubovich, etc.

Length of Gestation: A normal term gestation lasts 37 to 42 post-conceptional weeks with an accepted average of 40 weeks. Post-term is considered as from 43 weeks.

Chronological Age: (post-natal age) age estimated as from birth.

Post-conceptional Age: For the purposes of this document, this is the gestational age of a preterm baby, any time after birth and before 40 weeks of gestational age. It is calculated from the gestational age at birth, plus the number of chronological age weeks. For preterm babies beyond 40 weeks of gestational age, the corrected age is used. For example, a baby born at 32 weeks of gestational age is at 30 days of chronological age a post-conceptional age of 36 weeks.

Corrected Age: It is used in preterm babies after term. It results from subtracting the number of weeks for a birth at 40 weeks to the chronological age. For the same example, when this same child is 3 months of chronological age he barely is one month old in terms of corrected age.

Lubchenco Classification: The newborn infant is classified on the basis of weight and gestational age.

- Preterm Infant with appropriate size for gestational age (Preterm AGA): Preterm Infant whose birthweight lies between the 10th and the 90th percentiles for their gestational age;
- Preterm Infant small for gestational age (Preterm SGA): Preterm infant whose birthweight is below the 10th percentile for their gestational age;
- Preterm Infant with large size for gestational age (Preterm LGA): Preterm infant whose birthweight is above the 90th percentile for their gestational age;
- Term Infant with appropriate size for gestational age (Term AGA): Term Infant whose birthweight lies between the 10th and the 90th percentiles for their gestational age;
- Term Infant small for gestational age (Term SGA): Term infant whose birthweight is below the 10th percentile for their gestational age;
- Term Infant large for gestational age (Term LGA): Term infant whose birthweight is above the 90th percentile for their gestational age;
- Post-term Infant with appropriate size for gestational age (Post-term AGA): Post-term Infant whose birthweight lies between the 10th and the 90th percentiles for their gestational age;
- Post-term Infant small for gestational age (Post-term SGA): Post-term infant whose birthweight is below the 10th percentile for their gestational age;
- Post-term Infant large for gestational age (Post-term LGA): Post-term infant whose birthweight is above the 90th percentile for their gestational age.

Kangaroo Position: Vertical position of infant in direct skin-to-skin contact over a person's chest in prone position.

Kangaroo Position Provider: Person who holds the baby in the Kangaroo Position.

Primary Apnea of Prematurity Three types are described:

- Central apnea characterized by total absence of thoraco-abdominal movement (10 to 25% of apneas)
- Obstructive apnea characterized by absence of naso-pharyngeal air flow but thoraco-abdominal respiratory movements persist (10 to 25% of apneas)
- Mixed apnea, where obstructive apnea manifests before or after central apnea (50 to 75% of all apneas in preterm babies)

Breastfeeding: Feeding based on human breast milk, administered either directly from the breast or by previously expressing milk.

Direct Breastfeeding: feeding straight from the mother's breast.

Hind Milk: milk derived from end of sucking or from end of (mechanic or manual) extraction, which is richer in fat and calories.

Breastfeeding Supplementation: Use of formula to guarantee intake of the volume necessary for adequate growth.

Human Milk Supplementation: Use of vitamins. Supplementation of human milk with formula. Use of vitamins. Supplementation of human milk with formula.

Human Milk Fortifiers: Substances added to human milk to enhance nutrient contents, particularly protein, Ca and P

Kangaroo Adaptation: Period of adaptation to the different components in KMCM during which responsibilities are gradually transferred to the Kangaroo Position provider following the KMCM objectives.

Kangaroo Position Discharge: Hospital discharge that disregards weight or gestational age, with the baby in the Kangaroo Position to regulate temperature after a successful kangaroo adaptation.

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD

IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS

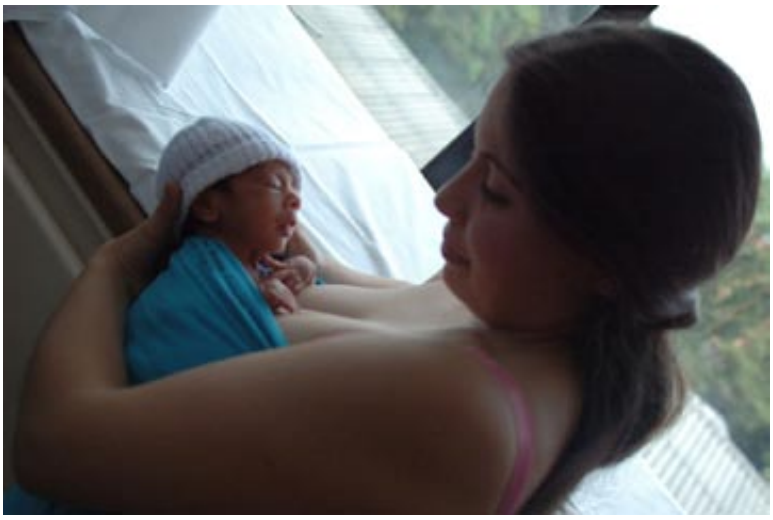

Photo by Alexander Moreno, Bogotá, Colombia

Evidence-based Answers

THE KANGAROO POSITION

Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine – Pontificia Universidad Javeriana

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Contents

1. THERMAL REGULATION

Question: **Can skin-to-skin contact between the infant's boy and the mother's chest (which takes part in the Kangaroo Position) provide a neutral thermal environment enabling temperature regulation in such a way at least as adequate as that of an incubator?**

Evidence-based Answer: **There is no significant difference between the capacity of the Kangaroo Mother Care Method position (KMCM) and that of the incubator to maintain an adequate temperature for preterm and/or low birthweight infants. The Kangaroo Position can be safely and effectively used until the preterm infant can regulate temperature by him/herself.**

Evidence Level: Randomized controlled clinical trials
Level of Consensus: Unanimous.
Rationale:

Preterm and/or low birthweight infants are not physiologically prepared to regulate and maintain an appropriate body temperature, it is therefore necessary to provide a neutral thermal environment that makes it possible for them to grow and complete the maturation process that could not finish in utero. By neutral thermal environment it is meant thermal conditions in which the energy expenditure (heat production) is minimal while maintaining inner body temperature.

Thermal loss in the preterm baby occurs by conduction, radiation, convection, and evaporation.

Loss by Conduction:
It is caused by direct contact of two solid bodies at different temperatures and do not tend to exceed 1% of the energy loss in preterm infants. Heat energy spreads following a gradient of temperature. Loss is limited if the solids in contact with the patient's skin do not differ greatly in terms of temperature with respect to that of the child. To this end, mattresses at a temperature of 36.5-37 are used. In the KMCM the temperature of the mother's skin may be the same or even higher than the child's and in this way heat is actively transferred until temperatures balance up; this means that no only loss by conduction is minimized but in addition it also warms the baby.

Loss by Radiation:
It results from a difference in the temperature between two bodies which are not in contact. Energy is transferred from the warmer to the colder body as electromagnetic radiation. In this way, as the difference between the child's skin temperature and the temperature in the incubator wall increases, so does the loss of radiation. This occurs frequently, since the temperature in the incubator wall usually lower than the child's. Additionally, the temperature in this wall tends to be higher than that of the room walls, which also adds to the loss by irradiation. If the temperature of the neonatal unit room is increased by 20-28 C, loss by radiation decreases by up to 50%. In the KMCM the baby's ventral surface is in contact with the mother's skin and does not radiate heat; the dorsal surface is covered by clothes or by the lycra band that keeps the child attached to their mother's chest and does not radiate heat either. Only small areas of the skin surface that are exposed to the air could radiate small amounts of heat, which means that it is crucial to cover them, especially the child's head, in order to prevent dissipation of heat by radiation.

Dissipation by Convection:
It is based on transferring heat energy to a fluid, usually gas (air). When the gas molecules run into warm skin, their temperature increase, and they are drawn away, being replaced by other cold molecules. A current of cold air coming closer to the skin is generated, which "steals" the heat, and as a result a current of warm air is produced, which is drawn away dissipating heat energy. For infants in incubators, thermal exchange by convention is related to the bulk of air in the incubator, the speed at which it circulates and its temperature; preterm babies will get warmer or colder by convection depending on the temperature at which the incubator keeps the air circulating inside. In the case of the Kangaroo Position (KP), the circulation of cold air around the baby's skin is limited by the lycra material and the cap covering their dorsal surface and head, while the air is heated by the conduction of heat from the mother's body.

Loss by Evaporation:
Evaporation is the most relevant potential source for energy dissipation: 0.58 Kcal per gram of evaporated water. The more immature the baby, the more significant the insensitive skin water loss. This increases when the central temperature is higher, in cases of a moisture lower than 50% or higher than 70% (increase from 30 to 80%), of crying or motor agitation (increase from 40 to 50%), of significant radiant heating (increase of 15%) or air draughts[1]. The loss may be reduced using a plastic cover but unlike other energy losses, it can never be totally eliminated.

Several studies have shown that an adequate neutral thermal environment may be preserved, either by maintaining the child in an incubator or using the Kangaroo Position. A randomized controlled clinical trial[2] based in three developing countries no differences were observed in the occurrence of hypothermia events when the kangaroo method was compared to the traditional care in an incubator. A study published by Ibe in 2004[3], comparing skin-to-skin contact versus incubator care in a cross-over experimental design, the risk of hypothermia was higher with the incubator (RR 0.09, IC 0.03-0.25). By contrast, Bosque et al. [4](id139) found a slight decrease in the temperature of babies using the Kangaroo Position. The fact that patients in this study did not wear caps during KP could explain the inconsistency of this result as compared with the other results observed. In fact, the other studies reviewed in the literature (Bergman[5], Ludington[6-10], Kadam[11], Acolet[12], Blaymore[13], De Leeuw[14]), including the meta-analysis by Chwo and Anderson[15]) agree that the Kangaroo Position is safe and effective in providing a neutral thermal environment for the infant and in preventing hypothermia events.

Not all babies are ready at any time during their extrauterine life to regulate their temperature adequately in the Kangaroo Position. Bauer y cols.[16-18] found that when the Kangaroo Position is initiated in the first week after birth, infants between 25 and 27 weeks of age develop hypothermia, which resolves in the second week after birth. Similarly, Bohnorst et al.[19;20] found a physiological lability associated with slight hyperthermia in very preterm unstable babies, while kept in the Kangaroo Position. Conversely, where babies are already stable despite being ventilated, they can regulate their temperature and their physiological parameters adequately, even those with the lowest weight[21].

2. GASTROESOPHAGEAL REFLUX

Question: **Is there any evidence that the Kangaroo Position prevents the gastroesophageal reflux?**

Evidence-based Answer: **No empirical data support that the Kangaroo Position prevents the GER. The Kangaroo Position seems not to favor the gastroesophageal reflux and it would be expected that frequency, duration and severity of the reflux episodes are less frequent than with other positions since the baby is constantly kept in a prone position, with their heads higher than the rest of the body, in an almost vertical position.**

Evidence Level: There are no randomized clinical trials supporting these recommendations, and evidence on this area is scarce. The assertion is based on anecdotal clinical observations, on patho-physiological reasons and on the analogy between the Kangaroo Position and the recommended anti-reflux positions (as the prone position or left lateral decubitus), where there are fewer, shorter episodes of GRE. In addition, a lower incidence of Gastroesophageal Reflux has been reported in breast-fed newborn infants, a practice favored by the Kangaroo Position and part of the Kangaroo Mother Method.

Level of Consensus: Unanimous

Rationale:

After swallowing, the bolus moves through the esophagus down to the stomach. The bolus remains in the stomach until the digestive process completes, and as it moves through the duodenum the chyle is constituted. The permanence of the bolus in the stomach depends on an anti-reflux system in the esophagogastric union acting as a barrier. This anti-reflux system is represented by the gastroesophageal sphincter, a high-pressure muscular area whose anatomical structure has yet to be verified. This high-pressure area constitutes the main element of the anti-reflux system since, had it not been present, the bolus would return to the esophagus when the intra-abdominal

pressure surpasses the intra-thoracic pressure. Although various mechanisms have been used to account for the presence or absence of the reflux, their true roles are controversial: 1) anatomical factors: acute His angle, size of the intra-abdominal esophagus 2) dynamic factors: maturation of the upper esophageal sphincter, esophagus peristalsis, gastric emptying and 3) chemical factors: GER-induced esophagitis and periesophagitis may prolong it.

Most of the GER episodes result from transitory and inadequate relaxation of the high-pressure area, which are apparently the same as those observed during the swallowing process to let food pass from the esophagus into the stomach. In neonates, factors such as the reduction of the basal tone of the gastroesophageal sphincter, transient increase of the intra-abdominal pressure (crying, coughing, pushing, movements or extrinsic compression, for example when changing diapers) and the hypotonia of gastroesophageal sphincter (passive reflux) come together.

Dhillon[22] reports survey results which show that GER is common in 77 neonatal units in the UK and that units vary greatly in terms of management.

Although no studies have directly assessed the relationship between the Kangaroo Position and the gastroesophageal reflux, it can be assumed that given the similarities between the Kangaroo Position and the studied and recommended position (prone position with an elevation of 30 to 45 degrees), the former may have a protective effect, since while the baby is in skin-to-skin contact over the mother's chest they are kept vertically and in a prone position during the day, and with an inclination of 30 to 45 degrees at night or while the mother is resting.

The prone position recommendation with an elevation of 30 to 45º is supported by empirical evidence. Current clinical studies show a trend in which this position reduces the number and the intensity of gastroesophageal reflux episodes in preterm babies. Tobin and Ewer [23;24] support these assertions in studies using various random positions, which favor the prone position – that resembles the Kangaroo Position, y and lying on the left side. They found a median reflux index of 6.7% in a prone position, 7.7% when lying on the left side, 12.0% lying on the right and 15.3% in a supine position. Oresntein[25] and Dellagrammatica[26] have seen better results with the prone position, which favored both a better emptying of the stomach and a reduction in the number of reflux episodes.

3. APNEA OF PREMATURITY

Question: **Is there any evidence that the Kangaroo Position protects against the apnea of prematurity?**

Evidence-based Answer: **No direct evidence that it prevents occurrence, frequency, or severity of the apnea of prematurity events. In physiologically stable infants, there is no evidence that the skin-to-skin contact (Kangaroo Position –KP-) increases the risk of apnea. For short periods and in stable patients, the frequency of apnea and periodic breathing is similar to that observed in these same babies while in incubators. There are no good quality data concerning continuous and prolonged Kangaroo Position, however, two randomized controlled clinical trials (CCT) apparently using passive surveillance (low probability for detecting apneas both in the kangaroo and control groups) do not report any differences in the frequency of apneas.**

There is no evidence supporting that kinetic stimulation (such as the one experienced by a baby in the Kangaroo Position as a result of the rhythmic–breathing- and non-rhythmic –walking, moving, etc.- movements) may be used for treating primary central apnea of prematurity or for preventing apnea episodes. However, tactile and kinetic stimulation is currently used as the initial measure for the preterm baby with an apnea episode.

Reports state that the Kangaroo Position is not well tolerated by seriously ill or physiologically unstable preterm infants [19;20]. For this reason, the group of authors in the present guide cannot recommend the implementation of the Kangaroo Position in a physiologically unstable child (which includes cases of apnea of prematurity). A stable baby tolerates manipulation (vital signs remain unaltered with appropriate manipulation), their vital signs are normal and stable, do not require pharmacological support and is not experiencing apnea, bradycardia, or hypoxia episodes.

Evidence Level: Good quality CCTs, before-and-after studies, CCTs with a low probability for detecting apneas, meta-analysis of ECC

Level of Consensus: unanimous

Rationale:

Introduction
The apnea of prematurity represents a serious problem both for its frequency on the first days of life and because in the most immature infants the condition may prolong for even weeks. It may, in addition, lead to serious consequences. The apnea of prematurity is defined as the cessation of breathing which jeopardizes alveolar ventilation, with a duration 20 seconds, or of any duration and accompanied by bradycardia of < 100/min and/or a fall in saturation with cyanosis[27].

There are three types of apnea: The central apnea is characterized by the total absence of thoraco-abdominal movements (10 to 25% of the apneas); in the obstructive apnea there is total absence of nasopharyngeal air flow but with the persistence of thoraco-abdominal respiratory movements (10 to 25% of the apneas) and in the mixed apnea the obstructive apnea develops before or after the central apnea (50 to 75% of the apneas).

Bradycardia episodes of < 100/min typically present after 10 seconds' breathing cessation and they are attributed to the hypoxia following the apnea. Occasionally apnea and bradycardia coexist and are the result of a vagal mechanism initiated at various starting points. When these bradycardia episodes are slower than 80/min, there is a decrease in the brain blood flow and they should be taken care of. Apneas with bradycardia generally present a few hours after birth, occasionally days, and their frequency is highest during the first week. Their presence alter 35 weeks of post-conceptional age is rare, however, they are always present in the evolution of infants whose birth took place prior to week 28[28].

The underlying patophysiology of these apneas with bradycardia may be accounted for by one or several of the following mechanisms:

- Immaturity of the cardiorespiratory system and its neurological regulation, which is more important the lower the gestational age. This immaturity involves all levels:
    - Respiratory centers at the medulla oblongata.
    - Vagal control of cardiac and respiratory automatism.
    - Chemical respiratory regulation (particularly immaturity of arousal before hypercapnia and mainly hypoxia).
    - Immaturity of oronasopharyngeal (narrow nasopharynx, hypotone of pharynx dilators), thoracic (diaphragm, intercostals) and alveolar (distant bronchioli, intrapulmonary shunts) receptors.
- It also accounts for the immaturity in other systems:
    - Influence over different sleep stages and their maturation.
    - Interaction between cardiorespiratory regulation by the autonomous nervous system and other functions based on this system: thermoregulation, arterial vasomotricity, motricity and digestive secretions.
    - Persistence of primitive reflexes before fear and pain (reflex vagal apneas and bradycardias)
- Maturation of these systems, which is not even complete in term infants at birth, explains development in terms of gestational age, respiratory and cardiac rhythm, duration and frequency of sinusal pauses and periodic breathing and apneas.
- Immaturity also leads preterm infants to react via apneas with or without bradycardia to insult or metabolic disorders. Consequently, all causes of secondary apnea should be ruled out or treated before relating the condition to immaturity.

The Kangaroo Position and Risk of Apneas in Unstable Children
Following reports claiming that the Kangaroo Position is badly tolerated by seriously ill or physiologically unstable preterm infants [19; 20], prima facie patients with apnea of prematurity should not be eligible for a continuous, prolonged Kangaroo Position.

Bohnhorst mentions a "before-and-after", non-randomized clinical study reporting similar frequency in the apneas between the Kangaroo Position and the incubator but more episodes of bradycardia and desaturation while infants were in the KP, not related with the changes in temperature. As the sample of infants studied included physiologically unstable preterm babies (in ICU, with apnea, desaturation and bradycardia before study entry and while in the incubator), this evidence may not be applicable to physiologically stable preterm infants in KP.

KP Protective Mechanisms against Apneas
One of the mechanisms that could explain why the Kangaroo Position prevents episodes of central apnea of prematurity lies in the fact that, while on the mother's chest, the baby receives rhythmic and episodic kinetic stimulation resulting from the mother's general as well as respiratory movements. Three meta-analyses studying the role of kinetic stimulation for preventing and managing apnea of prematurity find neither beneficial nor prophylactic nor therapeutic effects that may result from kinetic stimulation [29;30]. The maneuver under study was rhythmic stimulation by oscillating devices, which is not necessarily comparable (class effect) to the stimulation provided by the Kangaroo Position.

Another potentially protective mechanism in KP is related to the prone position, which apparently may be associated with better ventilatory mechanics and, as a result, with a possible reduction in the incidence of obstructive and mixed apneas. A cross-over randomized trial by Kurlak31 involving 35 preterm infants assessed effects of the incubator or crib position on the baby with apnea of prematurity. The results have shown a reduction both in the frequency as well as in the severity of very preterm babies in prone position. In a study involving 14 preterm infants with clinical apneas, Heimler[32] found that the supine position results in higher resistance to ventilation and more diaphragmatic fatigue; therefore, density of central and postprandial apneas as well as the frequency in periodic breathing episodes increase with this position when compared to the prone position.

Evidence that Continuous, Prolonged Kangaroo Position Does Not Increase the Risk of Apneas
Two CCT (Sloan[33] y Kadam[11]) assessing the effect of continuous, prolonged Kangaroo Position and observing both roomed-in mother-child were found and reviewed. Although both reports show that the frequency of apneas in patients allocated to the Kangaroo Position is the same or lower than controls, neither explicitly describes how presence of apnea was described (it probably implied clinical observation while providing the Kangaroo Position).

Evidence that Intermittent, Discontinuous Kangaroo Position Does Not Increase the Risk of Apneas
The results from many studies assessing physiological stability and quality of rest among preterm babies in KP suggest that while in this position not only frequency and severity of apneas do not increase[7;8;12;14], but rest periods are more adequate[34;35], physiological parameters are more stable and periodic breathing episodes are reduced[6].

Recommendations for Further Research:
Investigations assessing the effect of the type of kinetic stimulation provided by the Kangaroo Position on apnea of prematurity are warranted. Extrapolating the results obtained with devices that create oscillating movements in the crib or incubator may be inappropriate while it is reasonable to assess whether the rhythmic and sporadic movements the child experiences in the Kangaroo Position affect the risk or the frequency and severity of episodes of primary apnea, particularly the central type.

4. NEURO-PSYCHOMOTOR DEVELOPMENT

Question: **Is there any evidence that the Kangaroo Position has a positive effect on the neurological and psychomotor development of preterm and/or low birthweight infants?**

Evidence-based Answer: **The Kangaroo Mother Care Method seems to favor an adequate neurological and psychomotor development in preterm infants. Behavior, sleep/wake cycles and quality of rest are adequately organized and this is achieved earlier among similar babies not exposed to KP. Maturation of neurological and psychomotor functions as measured by standardized tests (Griffiths, Bailey) during the first year of life is more significant in some subgroups.**

Level of Consensus: unanimous

Evidence Level: Observational studies, few randomized controlled trials; however, all the evidence favors such statement.

Rationale:

Organization of Preterm Infant's Behavior and Sleep:
Studies on the impact of the Kangaroo Position over early, adequate organization of preterm infants' behavior and sleep have reported uniform results in babies with various degrees of prematurity. When in the Kangaroo Position, the infant quickly calms down and often falls asleep [10;35-37]. The infant sleeps more,[8] sleep is peaceful, breathing is regular, and active sleep[10;38] and arousal[38] decrease. Peaceful sleep episodes also occur when the infant is held by the father[39].

In addition to better and longer peaceful sleep, behavior is more organized while the infant is awake. Crying and irritability at wake while the infant is in skin-to-skin contact are rare. Overall, infants in the Kangaroo Position are calmer and cry less. [15;35](Bauer, 1998 521 /id.)

Ohgi (Ohgi, 2002 137 /id) reports results from a historically-controlled study, where preterm babies' performance during the Kangaroo Position was better at 40 weeks' gestational age in terms of irritability, visual-auditory orientation, their behavior at 6 months was more adequate and the neurodevelopmental scores (Bayley) at 1 year were higher. The Kangaroo Position also seems to have a positive effect on skills involving signal-sending and answering maternal requests [40;41].

The following mechanisms would explain this particular effect of the Kangaroo Position:

- Maternal heart sounds may induce sleep in the infant[42;43]; the Kangaroo Position lets the baby listen continuously to those sounds transmitted through the mother's chest wall.
- Fewer arousal episodes occur while preterm babies sleep in the prone position[44]. The Kangaroo Position implies holding the baby in a prone position over the mother's chest.
- Combining maternal heart sounds with soft swinging of the baby has a positive effect on the length of peaceful sleep in preterm infants[45-47]. The infant in the Kangaroo Position not only perceives maternal heart sounds but they are also exposed to soft, rhythmical swinging resulting from the mother's regular movements while breathing.
- Nesting preterm babies in a peaceful environment seems to decrease the number of arousal episodes while they sleep comfortably[48]. The lycra band and other types of support for the Kangaroo Position enable keeping the infant comfortably positioned (nested) between their mother's breasts.

Neurological and Psychomotor development:
Evidence derived from a CCT and analytical observational studies suggests that the Mother Kangaroo Method, and particularly exposing the mother-child dyad to the Kangaroo Position, improves performance in tests which measure psychomotor development[36;49-52].

Tessier et al.[36;49] suggest two mechanisms to account for the effect of KMCM on future psychomotor development in preterm infants.

- A Social Mechanism Involving Family Participation:

A main component of KMCM is parents' active participation (and empowering). This method strengthens the bond between the infant and the caregiver (usually the mother, the father and members of the extended family), making both more sensitive toward each other. It foster a family environment in which the mother feels more confident with her child and where the father is more involved in his child's home postnatal care. This maternal feeling of competence and parent's observed active participation represent a drastic change from the usual way parents' feelings and behaviors toward their preterm baby are handled, which could in turn enable extending this optimal neonatal and early infancy's setting to subsequent stages of the infant's life.

- Regulation of Brain Organization.

One of the most commonly documented findings in scanning imaging performed on preterm infants is the atrophy

of the corpus callosum, i.e. loss of myelinated fibers (white matter) connecting both brain hemispheres. Abnormal development (thinning or even agenesis) of the corpus callosum is associated with similar alterations to those documented in preterm infants, such as severe deficits of motor, cognitive and behavioral development, even at 1 year of age. Conversely, it has been observed that preterm infants with thicker corpora callosum have in turn a better motor development. The hypothesis that a preterm birth may delay or prevent the maturation of the corpus callosum may be then formulated, and this is associated with the neurodevelopmental disorders observed in preterm infants.

The statement by which infants receiving KMCM may present a better interhemispheric organization as a result of a reestablishment of the corpus callosum development, induced in some way by KMCM, is also hypothesized.

Current knowledge on the extraordinary brain potential to adapt to injury and on the therapeutic option to induce and regulate such plasticity to improve brain activation and function supports that hypothesis.

Post-natal plasticity is even more significant. Cell differentiation and synaptogenesis actually enable the suppression of aberrant pathways and the strengthening of normal, functional pathways. In these cases, a dramatic increase in the number of synaptic buttons per neuron is observed when, for example, rats are raised in complex environments or when both normal and preterm monkeys are stimulated. This brain potential for anatomic refinement may be the basis on which the kangaroo mother intervention operates to reinitiate and correct the maturation of the corpus callosum.

Additionally, specific environmental stimuli are required for a normal development. In KMCM the uterus is replaced by parents' bodies (instead of an inanimate, static incubator), which provide the sensory information necessary for developing the body's basic sensory-motor schedule. In fact, the Kangaroo Position enables the infant to receive plenty of sensory stimuli: auditory, through their mothers' voice and the usual heart sounds; olfactory, via the smell from the skin and breast milk; vestibular, through the position on the chest and the mother's multiple position changes; tactile, by means of the skin-to-skin direct contact; and visual, via the permanent visual contact with their mothers.

Carrying the infant in skin-to-skin contact could then foster neurobiologically programmed brain development during the last months of gestation. Although these long-term effects have not been confirmed in human infants, an intervention such as the Kangaroo Position is likely to have beneficial effects. In conclusion, the medium and long term effects observed in those receiving KMCM as to preterm infants' sensory-motor, cognitive and social development could be accounted for by neurobiological as well as social processes.

5. MOTHER-CHILD BONDING AND INFANT'S SECURE ATTACHMENT.

Question 1: **Is it important for the child that the mother establishes a connection (bonding) with them, and that the child develops a secure attachment with the mother?**

Evidence-based Answer: **This is apparently so. Empirical evidence is consistent with the hypothesis that the psychobiologically regulated series of transactions between the infant and the primary caregiver (mother), incorporated to the relationship seem to be very significant for an optimal development of self-regulation functions and for the organization of a "resilient" personality, with adequate stress management skills. Failure to establish a healthy connection on time may lead to future disorders in psychomotor, social, emotional and language development.**

Level of Consensus: unanimous

Evidence Level: Constructs and interpretations formulated by experts and supported by observational studies.

Rationale:

Mother-child bonding is a unique, specific relationship which is long-lasting and intense. This relationship has effects over the infant's physical, psychological and intellectual development[53-58]. In their developmental tasks, infants should learn to differentiate between trust and mistrust during the first two years of life, and develop a

secure attachment to their environment through an attachment to their mothers[59;60]. If the mother consistently responds to the infant's requests adequately and appropriately, satisfying their physical and psychological needs, the infant is more likely to learn to trust their mothers, see the world as a safe place, and grow as a secure person, capable of self-trust and trust in others, of cooperating and of being useful. By contrast, babies raised by mother not providing the necessary condition for developing secure attachment are at risk of delayed development of variables areas such as the emotional, cognitive, linguistic and social[59]. What's more, a non-attaching mother tends to ignore the baby and puts them at risk of neglect, abuse and non-organic failure to thrive.

Advances in knowledge and understanding of the development of brain functions allow the formulating the hypothesis that early experiences have a determinant role in the constitution of personality and adaptive functions of the ego[61]. These early experiences refer to the interaction between the child and their social environment, the relationship established with their caregivers (particularly the mother), by means of non-verbal communication enabling the reciprocal transfer of inner affective states, which in turn leads to bonding, an attachment between child and caregiver.

These environmental interactions have a structural influence on the last stage in the newborn's brain formation, where it is believed that the genetic information for neuronal organization does not suffice to achieve an optimal functioning of the central nervous system. In addition the hypothesis that environment-mediated experiences are critical for brain tissue differentiation per se is formulated[62]. Moreover, it is believed that the newborn infant's brain tissue is composed in such a way that it may be molded by the environment[63].

The early child's relationship mediated by attachment to their mother may be said to have both psychobiological and neurobiological consequences since to a certain extent this influence modulates the organization of the newborn infant's brain structure[62].

Social and emotional relationships between the child and their environment, occurring in a communicational context including facial and postural gestures, tones of voice, physiological and movement changes within attachment behaviors are experiences required for an early regulation of brain organization.

Question 2: **Are there critical periods for establishing a healthy bond? What if the establishing of bonds is altered or postponed in those periods (e.g. preterm birth)?**

Evidence-based Answer: **Bonding is established since the antenatal period and prolongs through the peri and post-natal periods. Hypotheses on bonding suggest the earlier the post-natal bonding the more likely the better bonding and its positive influence on the caregiver's parental skills and the development of a secure relationship by the infant. It is currently accepted that, despite particularly critical periods (such as immediate post-partum and subsequent hours), the empirical evidence suggests that they are not exclusive, their significance has been overvalued, and that they may be replaced by healthy remedial bonding, such as that established between foster parents and adopted children.**

Evidence Level: observational and quasi-experimental studies in humans, observational and experimental studies in animals, expert interpretations and non-systematic reviews of the literature.

Level of consensus: unanimous

Rationale[61]:

The most significant consequence of the critical appraisal of studies on bonding is Klaus and Kennell's change of viewpoint as regards the period of maternal sensitivity. In fact, while at first they stated there exists such a period[57;58;64], they subsequently claimed it has been speculated over the existence of a period of sensitivity of a few hours or days after birth. During this period of sensitivity, contact with the infant could trigger mother-child attachment[53;54] and actual contact after birth is not the only determinant factor for infants' further development, regardless of whatever may occur next. They also added that data suggest the existence of a particular period for mother attachment, its being particular in the sense that it occurs seconds after birth and that it could influence the mother's later behavior to her child at least during the first month after birth. Thanks to Klaus and Kennell change in their viewpoint some conclusions were made on which consensus is reached between those who support the "bonding" hypothesis and those who don't were formulated.

Firstly, the significance of the first hours after birth should not be overestimated. Bonding is a complex, dynamic process, influenced by significant number of factors varying over time. No single event (such as immediate contact after birth) has long-term consistently significant effects[65-67]. Besides, mothers and their children display a wide range of behaviors and interactions. In addition, skills required to look after an infant may be learned as shown by the differences observed between primiparous and multiparous women.

Second, the accumulation of evidence derived from studies both in animals and humans cannot prove nor abolish the existence of a short period after birth during which the mother is optimally capable of bonding with her child[68]. The many weaknesses of positive studies and the excessive amount of negative results in the remaining studies make it difficult to decide whether the mother-child contact immediately after birth is actually essential in generating maternal affection towards the child. Some authors believe that the empirical evidence is not strong enough to support the assertion that contact established immediately after birth has clinically significant effects in most women[65]. Under certain circumstances the contact seems to have an impact on some mothers[67;69].

Therefore, there is no irrefutable evidence supporting the idea that a contact immediately after birth is essential for later optimal development of an infant[70]. This does not mean that such contact is undesirable, simply because of its emotionally satisfactory nature for both mother and child[66]. Studies on maternal attitude and feelings derived from such contact show less maternal anxiety and more maternal self-trust even without a long-term effect on the mother-child relationship or on maternal behavior. As a consequence, the effect of the contact immediately after birth could become apparent in the mother's attitude and not in her behavior.

Question 3: **Is there any evidence that KMCM helps establish an earlier and better mother-child postnatal relationship?**

Evidence-based Answer: **Yes. The Kangaroo Position, and particularly the skin-to-skin contact, helps establish a healthy bond, or rather resume the bonding initiated during pregnancy and interrupted after neonatal separation of mother and child. Skin-to-skin contact reestablishes the mother-child relationship interrupted after the neonatal separation or initiates a caregiver-child relationship in a way that a more appropriate bonding and secure attachment are more likely.**

Evidence Level: CCTs, meta-analyses, before-and-after studies, case studies.

Level of Consensus: unanimous

Rationale:
The Kangaroo Position may be viewed as a method that not only enables physical contact between the infant and the caregiver but also modifies the environment surrounding the kangaroo baby, generating conditions in which parents are increasingly aware of their baby's needs and more willing to take responsibilities[36;49;71]. This optimal familiar environment stimulates the child, who in turn takes advantage of it.

The Kangaroo Position, particularly if provided continuously, helps transfer parents direct responsibility over baby care, and this makes them active participants for survival. Apart from allying parents to health care professionals aiming at child welfare, this responsibility and closeness reinforce parents-child connection, especially before a frail child. Clinical observations of the interaction between position provider and kangaroo baby suggest a bonding phenomenon in which the child's behavior reinforces parents' required skills to feed and stimulate adequately the baby's development[71].

This closeness adds a pleasant dimension for caregivers, who are empowered with feelings of responsibility and competence. There is empirical evidence cited in the bibliography on this positive effect of the Kangaroo Position over the mother's feeling toward her child[36;71-73].

A randomized controlled clinical trial assessing quality of mother-child bonding[71] documented that mothers in the Kangaroo Position group have better performance levels and proficiency in baby management, reducing anxiety possibly in connection to the maternal empowering associated with the intervention. The kangaroo group mothers received better support from their families but they reported to feel lonelier as a result of the degree of direct responsibility over baby care. As to feelings toward the child, babies seemed to depend more on the severity of

the underlying disease than on the exposure to the kangaroo intervention or control. Results have shown that the mother-child relationship was better in those mothers whose contact in the Kangaroo Position was initiated earlier (within the first three days).

An observational study (paired cohort) involving 73 patients[40; 73] showed that mother-child interactions improved at week 37 (positive affection, more caresses, adaptation to the child's requirements) and infants' response to stimuli was more adequate after receiving the kangaroo intervention. Mothers also controlled their emotions better. A stratified analysis by biological risk in newborn infants, mothers in the low risk subgroup reported less depression ($p < 0.0001$) and perceived their babies as less abnormal while the high risk subgroups presented differences between the kangaroo and control groups. In addition, at three months parents were more sensitive and provided their children with a better family environment ($p < 0.05$), and at six months the mother-child interaction was better for the Kangaroo Position group ($p < 0.01$). There was less depression in the group including mothers who provided the Kangaroo Position.

In terms of the psychosocial effects of the Kangaroo Position, the information on parents' immediate comfort or the child's development after receiving the Kangaroo Position is limited. The synthesis of published results focused on the immediate impact of the Kangaroo Position as to the baby's environment in the newborn care unit, both at the family level and in terms of the relationship with their mothers.

Impact on the Baby's Immediate Environment (initial separation):
The Kangaroo Position is often initiated after stabilization in the intensive care unit, is then continued in intermediate care and after discharge. The initial period of separation is usually considered an obstacle for parents/baby interaction since it prevents parents from carrying and touching the baby. Introducing the Kangaroo Position helps shorten this period and gives parents the chance to get actively involved in baby care. As the infant is in the Kangaroo Position, environmental noises are reduced as they are absorbed by the skin and their fathers or mothers' clothes. The Kangaroo Position could lessen the negative and stressful impact of the intensive care unit. Reports in the literature show that parents generally accept the Kangaroo Position uncomplainingly[2; 74], they feel closer to their children[3; 74] and feel satisfaction when carrying their babies in the Kangaroo Position[8; 11; 75]

Like other programs aimed at reducing environmental stress, KMCM could favor weight gain and mental development[76].

Impact on Home Environment:
The Kangaroo Position has a positive effect on home environment. The physical environment in the house becomes more stimulating, organized and open, and the father participates more. As mothers looking after more fragile babies are more receptive and more oriented towards their babies' needs, the family also turns more receptive to them. Both mothers as well as independent observers saw that parents encourage development in their babies making the environment more stimulating and adequate for them[49].

6. PHYSIOLOGY AND VITAL SIGNS

Question: **What is the influence of the Kangaroo Position over vital signs and physiological stability in preterm and/or low birthweight infants?**

Evidence-based Answer: **The Kangaroo Position in a stable baby maintains and even improves physiological stability.**

Level of Consensus: unanimous

Evidence Level: CCTs, before-and-after studies

Rationale:

Several authors have studied the impact of KMCM on preterm infants' physiology. The following items were studied: heart rate, vagal tone, respiratory rate, hemoglobin oxygen saturation, desaturation episodes, brain oxygenation, and metabolic markers (glycolysis, hormonal markers).

The results of these studies are limited and heterogeneous. This is due to the great variability in gestational ages of the preterm babies included in the studies, in the diseases and their severity at birth or when studied, and the diversity in the comparisons (incubator or cot versus skin-to-skin contact) and duration and frequency of KP in each study.

Despite this heterogeneity, the reported evidence suggests that the Kangaroo Position can maintain stability in vital signs and other physiological measures, and even the behavior of vital signs may be more stable as compared to controls (incubator or cot).

In stabilized preterm infants, oxygen saturation and respiratory rate are at least similar to those observed in controls[4; 11; 13; 14; 35; 77] and even respiratory patterns become regular with fewer episodes of periodic breathing[8], and the number of apnea and bradycardia episodes decrease[18]. Fewer hypoglycemia episodes have also been observed[5]. When the effect of differences in birthweight is controlled, beneficial effects on stabilization are more apparent in children 1000g (Fohe, 2000 134 /id).

Observations during the stabilization process of preterm infants suggest that the Kangaroo Position may be safe even during these periods of stabilization, and report that physiological endpoints were preserved between normal ranges during KP sessions (Ludington-Hoe, 1992 154 /id).

By contrast, at least one author reports that measure results do not favor the Kangaroo Position sessions in babies with instability and immaturity[19; 20].

Preterm infant stabilization could be more adequate in locations with scarce or poor quality technological resources. In a randomized trial based in Ethiopia, Woku75 showed that preterm infants allocated to continuous Kangaroo Position (24 hourly) had a lower mortality rate and required less time to stabilize than warmed babies managed in cots.

7. PAIN AND STRESS

***Question*: Does the Kangaroo Position ameliorate pain perception and harmful effects associated to pain procedures on preterm and/or low birthweight infants?**

Evidence-based Answer: **Immature newborn infants can perceive pain. Preterm and/or sick newborn infants undergo many painful and stressful procedures. Painful stimulation is repetitive in nurseries and the negative effect of these painful stimuli has been properly documented. Pharmacological analgesia, particularly opiates, though necessary clearly beneficial, are associated with many risks, especially during prolonged use. For all this, it is also necessary to use effective non-pharmacological measures for controlling pain, particularly before iterative painful stimuli.**

There is evidence showing that keeping the baby in the Kangaroo Position during a painful procedure reduces physiological alterations and facial gestures before pain in preterm babies, with no evidence of harmful effects.

Whilst pain alters both behavior as well as quality of sleep in preterm infants apart from increasing the intensity of their responses to new painful stimuli, the Kangaroo Position improves organization of behavior and sleep in this same population, and thus could alleviate negative effects of painful stimuli resulting from repetitive procedures on hospitalized preterm babies.

In sum, using the Kangaroo Position during a painful procedure is a possible effective and safe non-pharmacological measure to control pain. Given the positive effects on neurological organization in preterm babies, its systematic use at times other than painful procedures might counterbalance harmful effects of painful procedures on behavior and quality of sleep in these infants.

Evidence Level: before-and-after studies

Level of consensus: unanimous

Rationale:

One consulted source was the research thesis by Adriano Trespalacios-Prieto A, Piot-Ziegler C, Castelao E.'s *Douleur et naissance prematuree. Les bebes kangourous de Colombie*. 1-28. 2005. Laussane, Université de Lausanne[78]. summarizing results from various systematic reviews and including a search update until 2005. It was complemented with a search of published articles and systematic reviews, which identified some further publications.

Pain perception and consequences in the newborn infant
It has been long assumed that given that nervous system pathways in newborn infants are rudimentary, they should not conduct pain (since it is an elaborate sensation) and as a consequence painful procedures were performed without adequate use of analgesia and anesthesia. Infants' crying and whining were interpreted as reactions to fear or boredom [79].

The documents by Anand y Hickley[63; 80-82] from the 1980s showed that newborn infants, including immature babies, experienced pain and its deleterious consequences. Behavior alterations, facial gestures and crying accompanying painful or stressful procedures started to be adequately interpreted as clear signs of perceived pain.

The fetus can perceive pain. The development of the nociceptive system starts early during the intrauterine life: As from week 8 the first terminals for peripheral sensitivity start appearing in the buccal area; by week 20 skin sensory receptors are functional and by week 26 everything is set for the fetus to perceive pain. By week 30 thalamic fibers are fully myelinated and by week 37 cortico-thalamic fiber myelination is completed. Between weeks 15 and 26 pain perception and its intensity is unclear; using analgesic and anesthetic intervention for the fetus or the preterm infant is, if in doubt, the most ethical and adequate option.

It appears that infants are hypersensitive until the third months after birth. A more significant metabolic activity is detected in the newborn infant in those cortex and thalamic areas devoted involved in pain mechanisms, as compared to the subsequent months.

It has also been observed that when the child is repeatedly exposed to painful stimuli, they memorize them which generates a risk of altered interactions between the child and their environment until quite a time after the painful experience[63; 80; 83]. A study by Fitzgerald[84] shows that preterm babies between 26 and 32 weeks' gestational age undergoing repeated skin punctures on the foot to extract blood had a lower threshold for the flexion reflex as compared to the foot that had not been punctured.

Exposure to Painful Procedures
Immature or sick newborn infants often undergo various painful and/or stressful procedures: punctures, catheter and probe insertions, mechanic ventilation, etc. The negative effect of painful repeated stimulation has been clearly documented.[63; 80; 82; 83]

After a preterm birth, the infants remain in the hospital for several weeks. Neonatal unit environments are sometimes aggressive for sick newborn infants since painful, unpleasant diagnostic and therapeutic procedures should be performed. Pain also results from diseases or conditions such as post-operative trauma[85]. In addition, environmental stimuli, particularly if over long periods of time, are perceived as painful especially among the most immature babies[83]: continuous noise levels with peaks of over 100 dB, intense light (not varying between day and night), which could have a negative impact for future sleep organization and weight gain in preterm babies[86] and relate to neurobehavioral alterations even when there is no specific structural damage[87].

Frail newborn infants are often overstimulated and are exposed to potentially painful or stressful manipulation, which are frequent while they remain in hospital. The number of manipulations in an intensive care unit for specific management and testing could be as high as 130 events in 24 hours with rest periods ranging from 4 to 19 minutes[88].

Data about level of infant manipulation in sophisticated neonatal units (J. Hernández, Denver, CO, USA, personal communication) illustrate both the high frequency of manipulation and the fact its being inversely proportional to frailty: the more immature the infant the more interventions they undergo. The usual number of painful procedures during hospitalization according to Hernández is 60 to 100 and varies widely according to gestational age:

- Preterm babies 27 - 31 weeks: ~ 134 procedures
- Preterm babies < 27 weeks: ~ 300 procedures
- One preterm baby < 24 weeks ~ 488 procedures

Pharmacological analgesia, particularly using opiates, however necessary and clearly beneficial[89] is nevertheless associated to high risks, especially with a prolonged use[90]. For these reasons, non-pharmacological measures to control pain should also be used, particularly when painful stimuli are repeated.

Effects of the Kangaroo Position During a Painful Procedure

There is evidence showing that keeping the baby in the Kangaroo Position during a painful procedure reduces physiological alterations and facial gestures before pain in preterm babies, with no evidence of harmful effects.[91-93]

A randomized controlled trial in term babies[92] documented that the skin-to-skin mother/baby contact may reduce the perception of pain during a puncture on the foot. The times during which pain gestures (grimacing, frowning, closing the lids, or nasolabial line expression accentuation) and crying occurred were reduced by 65% and 82% respectively as compared to the control group. The high maternal cooperation index in the study suggests that this procedure may be easily applied in all hospitals.

Similar findings were documented among preterm babies of between 32 and 36 weeks' gestational age and 10 days from birth. Keeping babies in skin-to-skin contact 30 minutes before and during blood sampling by puncturing the sole reduces painful gestures and physiological changes associated to acute pain in the 90 seconds following the puncture[91].

Ludington et al.[93] report results from a cross-over randomized trial on physiological effects resulting from the pain derived from puncturing the sole in KP versus the same painful procedure in an incubator, in 24 preterm babies. Results show that heart rates ($P<0.012$) and crying times ($p<0.01$) were lower when the puncture was performed in KP compared to the incubator. Children slept more in KP than in the incubator.

Whilst pain alters both behavior as well as quality of sleep in preterm infants apart from increasing the intensity of their responses to new painful stimuli[83; 86], the Kangaroo Position improves organization of behaviour[94] and sleep[10] in this same population, and thus could alleviate negative effects of painful stimuli resulting from repetitive procedures on hospitalized preterm babies.

In sum, using the Kangaroo Position during a painful procedure is a possible effective and safe non-pharmacological measure to control pain. Given the positive effects on neurological organization in preterm babies, its systematic use at times other than painful procedures might counterbalance harmful effects of painful procedures on behavior and quality of sleep in these infants.

8. KANGAROO POSITION AND WEIGHT GAIN

Question: **What is the effect of the Kangaroo Position on somatic growth in preterm and/or low birthweight babies?**

Evidence-based Answer: **There is no direct evidence that the Kangaroo Position *per se*, continuously or intermittently, leads to better somatic growth results in preterm and/or low birthweight babies when compared to properly fed and managed babies in a neutral thermal environment and with a comparable health status. There is clear evidence that it has no negative effect on weight gain. When babies in the Kangaroo Position are compared to babies cared in suboptimal environments with cots or incubators that do not ensure a neutral thermal environment, the Kangaroo Position has been associated with better short and medium term growth and somatic development. Attributing this effect solely to the Kangaroo Position is difficult, since it is associated with the mother's presence and appropriate access**

to breastfeeding. Two randomized controlled trials found a discrete increase in head circumference growth, which could suggest that there is some protective effect of the Kangaroo Mother Care Method on cranial growth.

Evidence Level: **randomized controlled trials**

Level of Consensus: **Unanimous**

Rationale:

Since it provides a neutral thermal environment, the Kangaroo Position enables an adequate use of calories ingested for growth. If the physical location where the baby is kept provides an appropriate, neutral thermal environment (adequate fully functional incubators), usually no significant difference is observed in the rhythm and quality of somatic growth experienced by babies in the Kangaroo Position. Even when it has been claimed that skin-to-skin contact per se promotes further growth, regardless of other conditions, there is no empirical evidence supporting this assertion. Most of the evidence showing a better weight gain when the child is receiving the KMCM comes from randomized controlled studies based in developing countries, where hospital settings are often stressful and care equipment, including incubators, may not be fully functional. Although studies based in India[74], Zimbawe[95], Ecuador[33] or multicentric studies[2] (Mexico, Indonesia and Ethiopia) have documented better somatic growth among babies in the kangaroo trial arm, it is difficult to attribute this improvement to skin-to-skin contact per se or to a permanent and adequate thermal regulation in the Kangaroo Position, which associates to better breastfeeding-based nutrition with more frequent feeds and an adequate milk production, and a less stressful and painful situation for the baby. All this stands in contrast to babies managed in cots or incubators, where functioning conditions are not always optimal, they are separated from their mothers most of the time and receive little or no breast milk, and they are generally exposed to more stressful and less safe environments.

Allocation in the study by Kambarami[95] based in Zimbabwe was not randomized, weight measure precision was suboptimal (decagrams, to estimate differences in gram/day) and no significant differences were found between weight and length. In consequence, this report does not support the hypothesis that these babies in the Kangaroo Position gain weight more adequately. As to the multicentric study by Cattaneo et.al.[2], no differences for weight gain in the 2 locations with better access to a neutral thermal environment for controls (Mexico and Indonesia) were observed and were only documented for Ethiopia, where babies in the control group were managed in warmed cots and not in incubators.

At least two studies have documented that babies in the Kangaroo Position have a higher cranial growth as compared to babies exposed to control maneuvers. Rojas[96] reports that very immature babies in the Kangaroo Position 8 hours/day have a faster cranial growth than babies carried by their parents without skin-to-skin contact. Charpak et al. found a discrete but significant direct effect in head circumference for those term babies who were hypotrophic and preterm babies of various gestational ages and nutritional status in the continuous Kangaroo Position, as compared to control babies. No differences in weight, length or pondostatural gain rate are documented in this type of studies where the control intervention involves adequate nutritional intake (whether breastfeeding or not) and an appropriate neutral thermal environment is provided.

9. OTHER USES OF THE KANGAROO POSITION

1.1 The Kangaroo Position for End Stage Care

Question: **Does carrying a dying baby in the Kangaroo Position help the mother to cope with the painful situation and to go through bereavement more adequately?**

Evidence-based Answer: **No reports of studies or observations documenting the effects of carrying a terminal or dying baby in the Kangaroo Position were found in the scientific literature. Studies involving mothers with or without physical contact with their stillbirth suggest a lower bereavement quality in mothers with a physical contact. It is unlikely that these observations may be extrapolated to the effects of carrying a dying baby in the Kangaroo Position. In summary, there is no information indicating whether the effects of carrying a terminal baby in the Kangaroo Position are positive or negative.**

Evidence Level: Experts' opinion.

Level of Consensus: **Agreement (not all participants revised this item).**

Rationale:

This guide is not focused on an in-depth discussion of those processes and mechanisms involved in the parental bereavement for a newborn infant's death. However, the case of a baby dying while in the Kangaroo Position (particularly outside the hospital setting) should be considered. Besides, some neonatal units suggest that parents of critically ill babies, especially when they are to be weaned from artificial support, may carry their babies until they die. This contact may be reassuring and may help in the bereavement process. The fact that the parent caring the baby is actively involved in terminal care and could feel they are contributing something positive to their children is particularly valued. It is also sustained that it is an intimate, appropriate way to say goodbye to their children. Nevertheless, no specific evidence supporting these statements was found.

The literature search identified a study examining the effect of physical contact with the stillbirth on their mothers as to incidence of psychological disorders and difficulty in relating to other children born alive[97]. A secondary analysis of data gathered from a cohort study was performed. Mothers belonged to one of the following three categories: a) physical contact with the stillbirth's corpse, b) the mother only organizes the funeral and c) neither. Depression levels during the subsequent pregnancy were higher in mothers who carried their dead babies.

These results suggest that carrying a deceased newborn infant induces a more significant incidence of depression and a higher anxiety level in the subsequent pregnancy, and a higher post-traumatic stress level at 1 year. However, the situation is different for preterm births, and the observations from these studies cannot be extrapolated.

1.2 Transfer in the Kangaroo Position:

Question: **Is it safe and effective to carry newborn infants who have to be transferred to other healthcare institutions?**

Evidence-based Answer: **Yes. When adequate transfer incubators were unavailable in some places, the baby was transferred in the Kangaroo Position, with an adequate thermal regulation during the transfer. There is only one published report describing a satisfactory physiological stability in preterm and term babies transferred in the Kangaroo Position between hospitals. In absence of further evidence, the transfer in the Kangaroo Position cannot be recommended as a systematic practice or as a policy to replace transfer incubators. Instead it may be considered a safe and adequate alternative when transfer incubators are not optimal or are unavailable.**

Evidence Level: **Experts' opinion, non-comparative descriptive observational study.**

Level of Consensus: **Agreement (not all participants revised this item).**

Rationale:

It is an indispensable practice to ensure transfer in a neutral thermal environment when babies that do not yet regulate their temperature (immaturity, disease) should be transferred between healthcare institutions. Secure transfer should also be ensured for other conditions: physiological and metabolically stabilization, drugs, oxygen, ventilatory support, etc., according to the patient's needs. In addition, the vehicle for transport and the accompanying staff should be appropriate. This guide specifically addresses the role of the Kangaroo Position as an option to a transfer incubator. The Kangaroo Position enables babies' physical positioning with various advantages: neutral thermal environment, reassuring effect after the presence of the position provider -particularly the mother, the protective effect of the position provider's body against sudden movements and displacements, and the child's comfort when being carried instead of lying in a cot or incubator.

There is a descriptive study [98] involving 31 transfers of preterm and term babies: 18 were child's transfers to their original hospital (after receiving the treatments for which they were transferred), 13 were child's transfer to

the reference hospital to receive specific attention. The mother carried the baby in 27 events, the father in one, the nurse in two and the physician in one. HR, RR, hemoglobin oxygen saturation and rectal temperature were measured, and they remain stable during transport (10 to 300 minutes each event). Weight of transported babies varied between 1220 g and 3720 g. Parents felt comfortable and considered the transfer method positively.

1.3 Adoption and Kangaroo Position

***Question*: What is the possible role of the Kangaroo Position in the process of adoption of newborn infant?**

***Evidence-based Answer:* There is anecdotic evidence. For babies requiring the Kangaroo Position (preterm infants not regulating their temperature), the foster father or mother may (and should) provide the Kangaroo Position. If the baby does not require the continuous prolonged Kangaroo Position, intermittent skin-to-skin contact between the baby and their foster parents becomes all the same a way to attain physical acquaintance and to strengthen bonding.**

***Evidence Level:* Experts' opinion, reports by foster parents and substitute mothers.**

***Level of Consensus:* Agreement (not all participants revised this item).**

Rationale:

As stated previously (Chapter 5 on bonding and attachment), skin-to-skin contact has a positive effect on the relationship between the parents, but particularly between the mother and their babies. In the particular case of a newborn infant's adoption, the contact enables extraordinary bonding or its strengthening. Skin-to-skin contact allows for physical acquaintance between foster parents and their adopted child.

Recommendation for research agenda:

No publication on the potential use of the Kangaroo Position was found with the systematic search in the scientific literature performed for these guides. This could be part of the future research agenda, given that this area of investigation is completely open. There are no studies about this effect of the Kangaroo Position.

10. PRACTICAL RECOMMENDATIONS FOR THE KANGAROO POSITION

Based on the evidence-based responses as to properties, advantages and limitations of the Kangaroo Position, the group recommends the use of a standardized protocol of adaptation and maintenance of the Kangaroo Position in such a way that advantages for both babies and parents are maximized and inconveniences and risks are reduced. The following protocol to apply the Kangaroo Position is proposed.

1.1 Target Population:
These recommendations concern all preterm and/or low birthweight babies at birth, with weights < 2500 g (at birth or at some time during their extrauterine life), likely to benefit from the Kangaroo Position. The recommendations do not include skin-to-skin contact to healthy term babies, for whom the Kangaroo Position immediately after birth could help in coping with labor trauma, thermal regulation and promoting healthy bonding and successful breastfeeding.

Babies are eligible for the Kangaroo Position if the following criteria are met:

1.1.1 The baby is stable, i.e. vital signs and other physiological parameters (except temperature) remain normal during the manipulation necessary to place and keep them in the Kangaroo Position. When the baby is positioned in kangaroo for the first time, those physiological parameters should be monitored, at least clinically. Each institution should develop and use an initiation protocol for the Kangaroo Position defining eligibility and physiological stability. Acceptance and compliance with such protocol by the healthcare team in charge should be ensured.

1.1.2 Parents, and particularly the mother or the person appointed as main provider of the Kangaroo Position, should freely manifest their willingness to implement the Kangaroo Position once they have been adequately informed and their doubts and concerns have been carefully attended to. It is necessary to confirm such willingness after the mother has experienced the Kangaroo Position.
1.1.3 The Kangaroo Position providers should be free from these contraindications:
1.1.3.1 Contagious rash
1.1.3.2 Hyperthermia
1.1.3.3 Hypothermia
1.1.3.4 Skin wounds
1.1.3.5 Non-controlled epilepsy
1.1.3.6 Non-managed mental disease

1.2 Prerequisites for the Neonatal Unit

Care and administrative staff should be prepared and motivated. Mother/baby separation time should be minimized and appropriate physical interaction between parents and their baby (gradual, secure and supervised contact, according to the baby's clinical status, their maturity and physiological stability) should be allowed. Parents' access to the hospitalized baby should be easy and prompt, and access policies should be formulated explicitly: minimal restriction for parents' visits in terms of times and duration, local facilities for parents, and access to appropriate furniture (comfortable reclining chairs or similar), food, toilet, entertainment, etc. should be ensured. In short, the Neonatal Unit should be open and friendly. Adequate breastfeeding policies, supported by appropriate infrastructure and healthcare staff training, are desirable.

1.3 Place, Time and Mode of Initiation:

A basic condition before initiating KP is parental preparation, particularly the mother's, who should be aware of the benefits of KP for their babies and encouraged to be there most of the time. Practical aspects about a permanent or prolonged visit to the hospitalized baby are explained (including hygienic standards). This leads to a gradual logical transition from touching, caressing and finally carrying in the Kangaroo Position.

A nurse trained in the Kangaroo Mother Care Method identifies candidates to the position, in the maternity ward or in the mother's room (in cases of mother-child rooming-in) or among babies admitted to the neonatal unit. This member of the "kangaroo care team" contacts mothers and initiates family's sensitization to the kangaroo mother method. The mother is an ideal, main provider of the Kangaroo Position. In cases where the mother's health status makes her at least temporarily unavailable, the father may initiate the Kangaroo Position. Depending on the work load, this same person or a second member of the nurses' group in the kangaroo team may be in charge of initiating (after treating physician's judgment) the process of adaptation to the Kangaroo Position.

Once the mother-child dyad candidate to the Kangaroo Position has been identified and the motivation/ sensitization phase completed, the situation concerning the baby and the mother should be assessed to define when it is appropriate to start the process of adaptation to the Kangaroo Position. The idea is to implement the position as soon as it is possible, beneficial and with a minimum of risks. This may occur in the maternity ward for a preterm infant close to full term and for a vigilant and willing mother or may be delayed in immature or sick babies receiving intensive care. Recommending a specific date for the initiation may be inappropriate and should consider the mother-child dyad. During the adaptation, babies and mothers' tolerance of the Kangaroo Position is continuously assessed, and it is estimated whether to proceed gradually (intermittent Kangaroo Position, returning to a neutral thermal environment) or to proceed to a continuous, prolonged Kangaroo Position from the very beginning. Adaptation occurs in a hospital setting and over a variable period of time depending on the mother-child dyad's response to the Kangaroo Position. Stability in the baby's vital signs, breathing, arousal state, color, general aspect, posture and appearance of comfort or discomfort, presence of sleep/wake cycles, and general comfort during the position is assessed. The mother's attitude, tolerance, emotional state (whether she is at ease, stressed, etc.) is also observed. Based on these observations, carrying episodes are repeated more often and for longer periods until the mother can carry the baby adequately for indefinite periods, she feels more confident and secure, the baby tolerates it pretty well and the general status is appropriate.

When the mother is about to place the baby in the Kangaroo Position for the first time, she should be properly dressed (easy frontal access to the chest, for example by wearing a hospital gown worn backwards). Her nails

should be trimmed and cleaned, without any enamel, her body appropriately washed, particularly the area in direct contact with the baby's skin, her hair tied and she should not wear any jewelry, rings, cosmetics and perfumes. A support system, described later, should be provided to be able to hold the baby comfortably.

1.4 Outline of the Positioning and Maintenance of the Baby in the Kangaroo Position

Carrying the baby against the mother's chest avoids the baby's lying on one side, given that this posture is often associated with obstructive apnea especially among more hypotonic preterm infants. The kangaroo baby should be kept always upright, placed prone with their body and cheek against the mother's chest ("frog" position). The head should be turned to the other side in each feed (for example if the right cheek was against the chest, the head is turned so that now the left cheek is on the chest) and care should be taken that the airway remains free and patent.

Although the mother may keep the baby positioned with her arms, it is impossible to remain as such indefinitely. The baby should be maintained in the position using a device that can keep them in contact with the chest with little or no support from the mother's arms, and that is flexible enough to permit adequate movements, both respiratory or others. Many programs successfully use a single lycra-cotton band or binder that may be used both by the mother or father or by any other position provider. It may be lowered at any time to breastfeed or to change diapers or wash the baby. At the same time it allows the mother to move freely in order to perform routine activities related to her comfort, hygiene, nutrition, etc. without constantly depending on third parties. Closed lycra blouses or shirts are commercially available, they are known as lycra® "bodies" in many locations, and usually they are more comfortable in warm weather areas. The support system or "pouch" (band, binder or "body", or the most adequate and locally available device) should make the mother feel more secure but should not replace her monitoring the baby.

The Kangaroo Positioning process, especially when initiated, requires extreme care. An appropriately trained healthcare provider (usually a nurse) should help the mother or the position provider until they feel confident and comfortable carrying out the maneuver by themselves. In Intensive Care Units, the positioning should always be performed while a trained nurse follows a detailed and explicit monitoring protocol.

The mother should be trained in carrying the baby, ensuring easy, secure mobility. She should hold the baby with one hand placed behind the neck and on the back, letting the fingers reach the lower part of the jaw in order to prevent the head from slipping down and blocking the airway while the baby is in an upright position. The other hand should be placed under the baby's buttocks.

Where the baby is being oxygenated via cannula and/or is receiving intravenous liquids, another trained person (for example the father) should help the mother until she feels confident enough to do it by herself.

1.5 The Kangaroo Clothing

A cap made of cotton or wool, depending on the ambient temperature, is essential to avoid hypothermia episodes. The head should be covered with a warm hat to avoid temperature loss, given its significant surface in relation to the baby's body and because it is not protected by the binder.

The baby should wear a sleeveless cotton T-shirt or shirt, open on the front. The baby's back is protected in this way from heat dissipation and the baby's chest is in skin-to-skin contact with the mother's chest. The shirt might not be necessary in a properly warmed environment, particularly when the baby's back is always covered by the binder.

In warm humid environments, a cotton pad may be placed between the baby's face and the mother's skin surrounding the mother's neck, to absorb sweat and provide the mother some comfort.

Diapers are absolutely necessary to protect the mother and the baby from the baby's stools. The diapers should be sealed to prevent urine from filtrating, which by evaporation could cool the baby. This is not only uncomfortable for the provider but also irritates both the baby's and the provider's skins.

1.6 The Kangaroo Caregiver

Preferably, the mother should be the kangaroo caregiver given the positive effects of the Kangaroo Position on milk production and on the relationship between mother and baby. The father may nevertheless participate and help, especially when the mother needs time to look after herself, and to establish a father/child relationship vital for the baby's future. Other family members may become kangaroo caregivers since any healthy human being has an adequate thermal regulation able to maintain the baby's temperature. What really matters is to maintain the baby in skin-to-skin contact 24 hours a day.

The caregiver's position during the night is highly demanding and some individuals may see it as exaggerated and difficult to maintain. The caregiver should lie with at least a 30º inclination. Chairs in the neonatal unit should be

designed considering that position. At home a few bricks under the bed legs and using a binder can help parents maintain the baby's head higher and even so get to sleep.

1.7 Kangaroo Baby Care

The kangaroo baby should be constantly maintained in the Kangaroo Position, except when changing diapers and for breastfeeding. A lateral position is recommended when breastfeeding since skin-to-skin contact is preserved. This is important since breastfeeding periods may be prolonged particularly in the first phases of the kangaroo baby's care and above all for more immature babies that get easily tired when suckling.

As long as the baby requires the Kangaroo Position to regulate their temperature, no immersion baths should be given since this generates unwanted heat dissipation (in fact, they should not receive any bathing at all while in incubators). To bathe the baby a wet cotton swab should be used in areas that are likely to become dirty, particularly the genitalia and skinfolds, whenever necessary.

Carrying the kangaroo baby

The Kangaroo Position

Sleeping in the Kangaroo Position

1.8 Duration of the Kangaroo Position

Preterm and/or low birthweight babies are not "discharged" from the Kangaroo Position using external criteria; instead, they are meticulously observed until they "request" the discharge, i.e. when behaviors evidencing that the position is no longer necessary for thermal regulation, and that may even cause difficulty in heat dissipation are observed. Firstly, they are babies thriving adequately as evidenced by an adequate thermal regulation. When babies regulate their temperature without the need of thermal transfer by the position provider, they feel uncomfortable with the skin-to-skin contact. At first they become excited and try to get rid of the position while awake, and then both while wake as well as during sleep. They usually start crying and resisting when the mother tries to put them back in the Kangaroo Position after a change of diapers, they scratch the provider's skin, reject the position and try to set themselves free.

The adaptation to the Kangaroo Position starts during the baby's hospitalization, usually when they are stable and have overcome most of the serious problems derived from the transition to extrauterine life. These babies stay in the neonatal unit because they require a neutral thermal environment (growth or "gaining" phase in the incubator) and possibly some further surveillance. If such neutral thermal environment and adequate caring for the baby's nutrition needs as well as detecting changes and alarm signs could be ensured, discharging these babies from the hospital and managing them in the home would be appropriate.

This is precisely what results from mother-child dyads adequately adapted to the Kangaroo Position, where the mother feels confident, can properly feed and look after her baby and is always attentive and can recognize alarm signs in her child. The baby regulates their temperature while in the Kangaroo Position, remains stable and comfortable, and gains weight as well as they would do in an adequate incubator.

It is appropriate at this time to consider discharge from the Neonatal Unit while the baby is maintained in the Kangaroo Position. "Earlier" (or rather timely) discharge in the Kangaroo Position is adequate and secure provided adaptation was completed satisfactorily, the baby is stable and the mother or the position provider feels confident, can monitor the baby adequately, close medical surveillance is possible and, if required, the baby may receive appropriate emergency care.

Requirements for the home Kangaroo Position are the same as the hospital; the baby should be carried in the Kangaroo Position 24 hourly, the provider should sleep in a half-sitting position with a 30º elevation, and the family is requested to avoid visits to sick people, particularly those with infections. An earlier contact of the baby with their family environment, as it provides an ambulatory neutral thermal environment (the provider assumes the role of an ambulatory incubator), enables a faster integration of the child with their natural environment in the family and is one of the objectives of the kangaroo mother method.

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EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD

IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS.

Evidence-based Answers

Kangaroo Feeding and Nutrition Strategy

Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine – Pontificia Universidad Javeriana

Bogotá, 2005 - 2007

Contents

1. TERM INFANTS FEEDING

Question: **Is breastfeeding an optimal feeding method for term newborn infants?**

Evidence-based Answer: **There is a significant body of evidence supporting the assertion that maternal breastfeeding is the most appropriate and desirable feeding modality for healthy term newborn infants. Addressing this in depth or making recommendations as to the healthy term baby is beyond the purpose this guide.**

Evidence Level: Not applicable

Level of Consensus: Unanimous.

Rationale:

The following statements from the most recent official statement on feedings policies by the American Academy of Pediatrics –AAP-[1] stating the superiority of maternal breastfeeding and the specificity of breast milk could summarize the reasons why babies should receive their mother's breast milk: "Human milk is species-specific, and all substitute feeding preparations differ markedly from it, making human milk uniquely superior from infant feeding. Exclusive breastfeeding is the reference or normative model against which all alternative feeding methods must be measured with regard to growth, health, development, and all other short- and long-term outcomes. In addition, human milk-fed premature infants receive significant benefits with respect to protection and improved developmental outcomes compared with formula-fed premature infants."_

2. LOW BIRTHWEIGHT INFANT FEEDING DURING THE STABLE GROWTH PERIOD

2.1 Factors Conditioning Feeding Strategies for Preterm or Low Birthweight Babies

Question: **What are the factors affecting nutritional requirements and feeding modes for preterm and/or low birthweight babies?**

Evidence-based Answer: **Nutritional requirements and feeding modes and routes vary according to at least three groups of variables:**

- **Gestational age and birthweight and**
- **Comorbidity.**
- **Post-natal period which the baby is in,**

Evidence Level: Experts' opinion.

Level of Consensus: Unanimous

Rationale:

Introduction

Optimal growth and development levels are among the main aims of the recommendations on nutrient intake for preterm and/or low birthweight preterm infants. The determination of nutritional requirement for preterm infants, especially those with a low birthweight, (<1000 g) is based on limited data[2].

Maturity, babies' post-natal age and general health status (including the presence of specific diseases and/or complications) have an impact on the risks associated to feeding and condition and limit the feeding route to be used, nutrient tolerability and nutritional objectives.

Gestational Age and Birthweight

Nutritional requirements for the same post-natal period vary according to maturity (gestational age) and quality of intrauterine nutrition (adequate weight, high or low for the gestational age). Although the Lubchenco classification[3;4] has been traditionally used to describe these infants, there may be extreme variability in the same category (e.g.

preterm infant adequate for the gestational age), with very different nutritional requirements (e.g. 26-week or 35-week preterm babies in the same category). It may be more adequate to consider absolute birthweight and gestational age since extreme preterm infants (less than 28 weeks) or very low birthweight infants (less than 1000 grams) have limitations and variable nutritional requirements as compared to a moderate preterm infant of 32 weeks and weight close to 1500 g. These variations become more significant in the case of preterm babies close to full term of more than 34 weeks of age, even when they are "preterm infants adequate for the gestational age".

Recommendations for nutrient intake may be insufficient for some and excessive for others. Nutritional requirements in newborn infants of different maturity and weight categories are not homogeneous, even within each category. Therefore, the nutrient administration should be tailored considering enteral tolerance, metabolic tolerance, restrictions imposed by specific health conditions and requirement related to development status[2]

Co-morbidity
Possible changes in the nutritional requirements and modes of administration related to morbid states concomitant with prematurity or low birthweight are potentially unlimited: acute/chronic infection, congenital malformation, trauma, errors of metabolism, etc. The description of kangaroo nutrition strategies and problems in infants with different concomitant conditions is out of the scope of the present guides, and instead they are limited to general cases. Therefore the changes in the nutritional requirements associated to comorbidity are not discussed in this document.

Post-natal Growth Periods:
Preterm infant requirements and the limitations to meet them vary according to the post-natal stage the infant is in. Overall, three significant periods are described: transitional, stable growth and post hospital discharge

Transitional Growth Period.
The transitional period[2;5-7], from birth until the main aspects of immediate and mediate transition to extrauterine life are completed (usually from day 0 to day 10), where parenteral nutrition support and/or the use of strategies of adaptation of child's physiology to the use of the digestive tract for administering the nutritional requirements may be necessary.

During the transitional period, survival is a priority when managing preterm and low birthweight infants. Given babies' immaturity and the many life-threatening conditions they may have to face, the aim of nutritional intake at this stage can be limited to providing indispensable calories and nutrients to preserve life, even at the expense of growth.

Revising rationale and evidence on which feeding strategies for babies in the transitional period are based are out of the scope of these guides. Those strategies are aimed at balancing estimated nutritional requirements for transitional or sick babies against physiological limitations imposed by immaturity and disease. Nutrition during the period of adaptation to extrauterine life usually involves the gradual transition to non-oral feeding modes (parenteral nutrition, enteral nutrition) and oral feeds. These modes take into account maturation of the digestive system as well as other systems: ability to digest and absorb different nutrients, gastrointestinal and systemic (circulatory, renal) tolerability of osmolal loads and volumes, gastric emptying; and are particularly aimed at reducing weight loss and proteic catabolism in preterm babies by giving "aggressive" nutrition, usually parenteral and including an adequate protein intake.

Even when the (gradual, intermittent or continuous) Kangaroo Position may be initiated during the transitional period, the feeding modes during the transitional period are not included in the feeding and nutrition strategies. The guides are centered on discussing feeding strategies appropriate for babies who have completed the transition.

Stable Growth Period
The "stable growth[2;5;7]" period occurs between the end of the transition and until the preterm baby reaches full term. For the preterm baby this stage is equivalent to the intrauterine growth period they would have gone through had they been able to reach full term[6], and for whom enteral nutrition modes, particularly the oral route, is usually appropriate.

These babies, completing the transition and successfully adapted to the Kangaroo Position (eligible for discharge

from the neonatal unit while in the Kangaroo Position), go through a phase in their extrauterine life in which ideally growth should only occur at the rate it would have proceeded had they remained in the uterus, but instead they should first make up for deficiencies accumulated during the transitional period. Nutritional requirements for this period have been estimated based on intrauterine growth curves and on nutrient accumulation rates despite the fact that current trends point to also considering growth and medium and long term development results[8].

For these infants with a reasonable clinical stability and tolerability to enteral –preferably oral- feeding, the main feeding objectives are a) recovery of growth until reaching a body size adequate for the corrected age and b) normalization of body composition.

Post-discharge Growth Period
This last period extends until the baby reaches full term (regardless of whether they are discharged from the hospital or not) until 1 year of chronological age[5].

The objective of the present guides lies in feeding strategies during the "stable growth" period and no mention will be made of strategies appropriate for the transitional or the post-discharge growth periods.

2.1 Energy and Macronutrient Requirements for Low Birthweight Newborn Infants.

Question: **What are the energy and macronutrient requirements for preterm and/or low birthweight babies?**

Evidence-based Answer: **Energy and nutrient requirements are variable and have been estimated by kilogram of weight and by the period the patient is in[1;5-7;9-11]:**

Energy: **preterm babies require a lot of calories to reach growth rates similar to those in the intrauterine life during the third trimester. Energy requirements vary greatly according to the baby's conditions and diseases, the period in which they are in (transitional or growth) and the feeding route (parenteral, enteral). The requirements are generally lower during transition and with parenteral feeding.**

Protein: **Protein is administered to provide appropriate quantity and quality and thus ensure adequate nitrogen accretion and at the same time avoid metabolic stress.**

Protein/Calorie Intake Ratio: **The recommended ratio between total calories and protein to efficiently profit from the protein administered and to promote fat-free body mass gain is about 2.5 to 3.6 g per 100 Cal[5].**

Babies completing the transitional period with an accumulated post-natal nutritional deficit (intrauterine or post-natal stunted growth, not attaining catch up growth) should receive more protein and an adequate calorie/protein ratio in order to maintain appropriate growth rates and recover from accumulated nutritional deficiencies.

Carbohydrates: **Carbohydrate minimal requirements based on the need to fulfill brain energy requirements while glyconeogenesis and ketosis are kept to a minimum are 11 to 12 g/Kg/day.**

Lipids: **The main dietary source for preterm babies is fat (40-60% of total calories). Fat requirement mainly depends on energy requirements and protein and carbohydrate intake. Essential (omega-3 and omega-6) fatty acids are necessary for cell membrane function and development of the nervous central system.**

Evidence Level: Experts' opinion.

Level of Consensus: Unanimous

Rationale:
Preterm babies invariably present some malnutrition, at least for a certain period of time, as compared to the fetus, usually receiving generous and uninterrupted nutrient flow. Nutritional support should be aimed at minimizing the time during which preterm babies receive nutrients in a suboptimal fashion.

Fetal calorie and nutrient requirements are described in Table 1.

Recommendations for nutrient intake during the transitional and stable growth periods are based on fetal nutrient consumption but are standardized for "typical" preterm newborn infants. For example, the recommendations made by the group of experts in the Life Sciences Research Office[5] are addressed at preterm babies (less than 36 weeks) during the stable growth period (until reaching 1800-2000 g), and they are based on studies involving babies generally with a birthweight higher than 750 g. For estimation effects they use a "standard preterm infant" with a weight of 1000 g, consuming 120 Cal/kg and receiving a volume of 150 ml/Kg. Despite the recommendations by post-natal age, there is no evidence that post-natal age or maturity (gestational age) during these early periods of extrauterine life (transition and stable growth) determine or affect nutrient requirements, and instead the latter depend on body mass and growth rates[11].

Table 1. Nutrients Estimated to Attain Fetal Growth Rates [11]

Weight (g)	500– 700	700– 900	900–1200	1200–1500	1500–1800
Fetal weight gain (g/d)	13	16	20	24	26
(g/kg/d):	21	20	19	18	16
Protein (g) NX6.25)					
Obligatory loss	1.0	1.0	1.0	1.0	1.0
Growth	2.5	2.5	2.5	2.4	2.2
Required intake					
Parenteral	3.5	3.5	3.5	3.4	3.2
Enteral	4.0	4.0	4.0	3.9	3.6
Energy (Cal)					
Loss	60	60	65	70	70
Basal expenditure	45	45	50	50	50
Other expenditures	15	15	15	20	20
Growth	29	32	36	38	39
Required intake					
Parenteral	89	92	101	108	109
Enteral	105	108	119	127	128
Protein/Energy (g/100 Cal)					
Parenteral	3.9	4.1	3.5	3.1	2.9
Enteral	3.8	3.7	3.4	3.1	2.8

Table 2 summarizes the recommendations by different sources for the transitional and stable growth periods.

The individualization of nutritional care for infants in the stable growth period is necessary because babies step out of this period under variable circumstances and in variable states, resulting from pregnancy and labor conditions and the difficulties experienced and managements received during the transitional period. From the point of view of somatic growth, at the onset of the stable growth period newborn infants may fall under one of the following categories[12]:

- Babies with an adequate birthweight and weight for their post-conceptional age (appropriate growth during the transitional period) at the end of the transition.
- Babies with an adequate birthweight for the gestational age (AGA) but on completing the transitional period have a low weight for the post-conceptional age or for the corrected post-natal age (post-natal stunted growth).
- Babies with a low birthweight for the gestational age (GA) but whose weight on completing the transition was appropriate for the post-conceptional age (early catch-up growth)
- GE babies who remain thus on completing transition (Intrauterine growth restriction –IUGR-, uncorrected during transition)

Table 2. Typical Nutritional Requirements for Preterm Newborn Infants inTransitional and Stable Growth Periods[2;5;7]

	Route	Day 1	Transition	Growth
Energy (Cal/Kg/d)	Parenteral	40-50	60-70	90-100
	Enteral	50-60	75-90	110-135
Protein (g/Kg/d)	Parenteral	2	3.5	3.2-3.8
	Enteral	2	3.5	3.4-4.2
Protein (g/Kg/d)	Parenteral	7	5-12	9.7-15
	Enteral	7	5-12	7-17
Lipids:	Parenteral	1	1-3	3-4
(g/Kg/d)	Enteral	1	1-3	5.3-7.2

Babies in the transitional period with accumulated post-natal nutritional deficit (groups 2 and 4 listed above) should be given more protein and an adequate energy/protein ratio to maintain appropriate growth and recover from accumulated nutritional deficits.

Energy: A positive caloric balance is necessary to promote growth: intake should surpass basal energy expenditure and other essential losses. Energy expenditure in preterm babies[7] comprises the basal metabolism (47–52 Cal/kg/d), exercise expenditure (3–4 Cal/kg/d), energy expenditure resulting from output, mainly fecal (11–18 Cal/kg/d) and growth energy expenditure, which is variable.

On average the baby gains 1 gram in weight every 3-5 retained calories ; 2 cal per gram are needed to accumulate fat-free tissue; 7 cal per gram are needed to store adipose tissue, of higher caloric density.

Based on these considerations, energy intake for preterm infants receiving formula has been estimated in 98-128 cal/Kg/d (*ESPGHAN 1991*) and 105–130 cal/kg/d (*American Academy of Pediatrics (AAP) Committee on Nutrition 1998*).

Protein: The protein intake target should result in an optimal nitrogen retention, without adverse effects on metabolism, such as uremia. When results from studies on fetal nitrogen uptake together with physiological, biochemical, neurodevelopmental and somatic growth data are considered, the minimum protein intake is established as 3.4 g/Kg/d for preterm babies[5]. Side effects occur when 5 g/Kg/d or more are administered. Although the protein content in preterm formula is high, it is probably insufficient to maintain growth among small preterm babies (particularly those with an extremely low birthweight) at a rate similar to those of intrauterine growth[13-15].

When protein intake requirements to maintain a neutral nitrogen balance (0.75 g/Kg/d), intake to increase fat-free body mass (0.75 g/Kg/d) and accumulated growth deficit are considered, recommendations for protein intake increase, as shown in Table 3.

Table 3. Recommendation on Protein Intake and Protein/Energy Ratio for Preterm Infants according to Post-conceptional Age and Need of Catch-up Growth[6]

Need of catch-up growth Period	No	Yes
26-30 weeks PCA[1]: 16-18 g/kg/d FFM[2]	3.8-4.2 g/kg/d PER[3]: 3.0	4.4 g/kg/d PER[3]: 3.3
30-36 weeks PCA[1]: 14-15 g/kg/d FFM[2]	3.4-3.6 g/kg/d PER[3]: 2.8	3.6-4.0 g/kg/d PER[3]: 3.0
36-40 weeks PCA[1]: 13 g/kg/d FFM[2]	2.8-3.2 g/kg/d PER[3]: 2.4-2.6	3.0-3.4 g/kg/d PER[3]: 2.6-2.8

[1]PCA Post-Conceptional Age; [2]FFM Fat-Free Mass; [3]PER Protein/Energy Ratio (per 100 cal)

From Rigo J, Senterre J. Nutritional needs of premature infants: Current Issues. The Journal of pediatrics 2006 November;149(5, Supplement 1):S80-S88.

Protein/Energy Intake Ratio: When the energy intake is not enough, the body uses protein as a source of energy. When too many calories with a limited protein intake are administered, the surplus of energy is then stored as fat. If the protein/total calorie ratio is adequate, fat-free body mass is built up. The recommended protein:calorie ratio varies between 2.5-3.6 g per 100 cal[5] to 2.8-3.8 g per 100 cal[11].

Carbohydrates: They represent an important source of energy and the main fuel for the central nervous system. Carbohydrates are also used in intermediate metabolism, mainly for lipid and non-essential amino acid synthesis in the liver.

Lipids: Caloric density in fat is the highest of all energy nutrients: 9 cal per fully oxidated gram. Thus it becomes the main source of energy available in breast milk and formula. In addition, essential fatty acids (omega3 and omega6) should be administered exogenously to enable an appropriate cell membrane synthesis and function, an adequate arachydonic acid (eicosanoid) metabolism and an proper development of the central nervous system. Variability of fat content in breast milk, either term or preterm, is very high and this variability is observed between one mother and another, among different hours, and between the beginning and the end of a feed, in such a way that it has been claimed that non-fortified breast milk is a little reliable source of energy as fat[15]. Nevertheless, lipid profile and their digestibility is clearly superior to any other source of oral or enteral nutrition.

2.1 Calcium and Phosphate Requirements for Preterm and/or Low Birthweight Infants.

Question: **What are the Calcium (Ca) and Phosphate (P) requirements for preterm and/or low birthweight babies?**
Evidence-based Answer: **Ca and P requirements depend on gestational age at birth. Bone mineral content in preterm infants is much lower and considerably higher intakes are required. Some osteopenia always occurs in preterm babies since Ca and P intake systems in extrauterine life cannot match the efficiency of placental transfer. Intake may not reach intrauterine mineral accretion rates but at least should prevent severe osteopenia and its risks.**

Ca and P intakes necessary to ensure adequate bone health and development in preterm infants, particularly for very low birthweight infants (1500 g), are controversial. However, and based on the assertions mentioned above, the most reasonable recommendation for the stable growth period in these infants 1500 g at birth is the administration of highly absorbable Ca 100 to 160 mg/Kg/d and P 60 to 75 mg/Kg/d, resulting in a Ca retention of 60 to 90 mg/Kg/d, which can eliminate the risk of fracture and osteopenia clinical symptoms. In most infants >1500 g (very low birthweight and close to term infants), Ca and P intake attained with breast milk would be enough to present severe osteopenia.

Evidence Level: Expert's opinion, basic studies in animals, biomedical studies, and controlled and uncontrolled observational clinical studies in preterm infants.

Level of Consensus: Unanimous

Rationale:

Introduction
The main minerals necessary for bone formation are calcium (Ca), phosphate (P), magnesium (Mg) and zinc (Zn)[16]. As to Ca and P metabolism, the fetus has to fulfill two requirements: a) maintain physiological levels of Ca and P in body fluids, particularly extracellular ionized Ca levels necessary for the stability of fetal physiology (cell membrane function, blood clotting, etc.) and b) ensure an adequate provision for skeleton mineralization.

Neonatal adaptive alterations of Ca and P levels (e.g. hypocalcemia and its manifestations, hypercalcemia, etc.) do not at first sight depend critically on nutritional intake of these minerals, since maintaining adequate levels in the extracellular liquid compartment may be attained by transferring Ca and P from bone reserves, apart from controlling intestinal absorption and renal excretion, these mechanisms being mediated by hormones involved in calcium metabolism: parathormone, calcitonin and calcitriol (vitamin D 3).

On the other hand, an insufficient intake of Ca and P is clearly and directly associated to bone mineralization disorders in both preterm and term babies, even when levels and activity of calciotrophic hormones including vitamin D are normal. As a result, the determination of pre- and post-natal nutritional requirements of these minerals is related to success or failure in bone mineralization.

Thus the present discussion is centered on the role of Ca and P for an appropriate bone mineralization. Physiology and alterations of the regulation of Ca and P levels in body fluids will not be examined.
Bone mineralization, Ca and P during fetal life
While bone development starts early in embryonic life, bone mineralization mainly occurs during the third trimester of pregnancy, which gives the fetus an average accelerated longitudinal growth of about 1.2 cm/week during the third trimester of pregnancy[6]. Fetal skeletal growth and bone mineral accretion not only depend on transplacental intake of energy, protein and vitamins but they are also directly affected by net transfer of calcium and other minerals from the mother to the fetus. From the second trimester onwards, calcium and phosphate serum levels are about 20% higher in the fetus than the respective maternal levels[17]. The fetus's environment is rich in estrogen and calcitonin, and it is hypercalcemic, which makes balance between bone Ca deposition and resorption lean to Ca bone deposit and bone remodeling, and in turn to a thicker bone cortical.

Additionally, fetal movements against the wall of the uterus stimulate Ca deposition and modeling. Both mechanic loads the bone carries during intrauterine life (normal fetal movements against the wall of the uterus) as well as muscular tone and mass development appear to be significant for an adequate fetal bone mineralization. In fact,

the reduction of fetal movements and the poor development of muscular mass are associated with long bone osteopenia and may even result in pathological fractures during infancy[18].

By the end of a normal pregnancy, the fetus has between 13 and 30 g of Ca (average 21 g) and about 16 g of P, of which approximately 98% and 80% respectively are contained in the bone[6;16;19;20]. These proportions remain unaltered during life till old age[19]. Mineral accumulation starts during the second trimester and reaches a peak during the third trimester. By week 20 fetal Ca accumulation is about 50 mg/d and increases up to 330 mg/d in week 35[16;20]. Eighty percent of the intrauterine accretion of Ca occurs during the third trimester[20] and in this period approximately 200 mg/d are retained on average[16]. The Bone Mineral Apparent Density –BMAD- (Bone are/Bone Mineral Content) estimated by dual-energy X-ray absorptiometry (DEXA) increases during the third trimester, which indicates that rather than bone growth, mineral accretion rate is faster by the end of a term pregnancy and as a result, the full term newborn infant's skeleton has a high proportion of mineralized bone.

As a consequence of these processes, skeleton density in the full term newborn infant is high (amount of bone mass per bone volume unit), particularly given the thick cortical and the comparatively small medullar cavities, apart from an adequate mineralization.

Post-natal Bone Mineralization, Ca and P
After a term birth, the accumulation of Ca and P necessary to maintain somatic and skeletal growth remains to be high during the first months of post-natal age, and is gradually reduced as age increases. Accumulation rates of these minerals during the first months of life are about 140 mg/d for Ca and 70 mg/d for P. In term babies, the placenta in the antenatal period and breast milk in the post-natal period are good adequate sources to maintain these accumulation rates.

There is a sudden interruption in the flow of nutrients at birth, including Ca and P. From then on, to maintain mineral homeostasis the newborn baby depends on intermittent absorption through the gastrointestinal tract and on adequate accumulation and metabolism.

The hypercalcemic fetus becomes a relatively hypocalcemic infant, which triggers PTH secretion. There is a reduction of the large amounts of Ca available to the fetus for bone mineralization. As a matter of fact, bone Ca starts to play an important role in maintain normal calcium levels. Additionally, there is a change in the mechanic stimulation since movements by the infant find less resistance than the fetus confined within the uterine walls. There is a discontinuation of estrogen provision and other hormones increasing Ca bone retention.

As a consequence, the infant's skeleton should adapt to this new environment, with less accretion and modeling and more bone resorption. Long bone density is reduced by 30% during the first 6 months of life, particularly due to the increased size of medullar cavities with relative thinning of the cortical bone. In term infants, this condition is known as "physiological osteoporosis of infancy", which might be an unfortunate way to call it since there is no increase in bone fragility[6].

Ca retention, and body content, are determined mainly by intestinal absorption. The absorption of Ca occurs in the small intestine, and represents around 60% of the calcium ingested in breast milk in term infants. Absorption of supplementary Ca added to breast milk through commercially available fortifiers resembles the absorption of calcium naturally contained in breast milk[19]. The calcium filtered in the kidneys is then reabsorbed through the nephrons but mainly in the proximal convoluted tubules and Henle's loops. In children and adults calcium resorption is very efficient and most of the filtered calcium is reabsorbed. By contrast, renal resorption of calcium is much lower in the neonatal period and particularly among preterm infants, with urinary Ca/creatinine ratios as high as 0.75-1.32 in preterm infants <1500 g at birth[19]. Furosemide, acting at the level of Henle's loop, significantly increases renal excretion of Ca. Preterm infants, particularly when receiving furosemide and a high intake of Ca, are at risk of hypercalciuria and renal calcification[21]. On the contrary, thiazide diuretics reduce calciuria.

Intestinal absorption of P takes place in the jejunum and depends both on P intake and proportion of administered Ca and P. When the levels of one of them is very high, the absorption of the other is reduced. At first P absorption is very efficient (90% of the P administered in breast milk, 72% in formula) and is not limited by hormones or vitamin D. Phosphate balance depends then on renal resorption or excretion. Around 90% of the filtered phosphate is reabsorbed. In neonates phosphaturia is low basically because the glomerular filtration rate is low as compared to those observed in other ages.

Bone Mineralization, Ca and P in Preterm Infants

Since most of the calcium accretion occurs during the first trimester, the body calcium content and bone mineral content are insufficient in preterm infants at birth: while a term infant has around 30 g of calcium, 24-week fetus has only 3 to 4.5 g of calcium. The earlier the birth, the more pronounced the body calcium deficiency. It may be ascertained that any preterm infant has Ca and P deficiencies at some time during their post-natal growth.

In fact, the skeletal adaptation to the extrauterine environment described above for term babies occur earlier and more intensely than in preterm infants[22]. A preterm birth interrupts fetal bone mineralization which, together with the dramatic reduction in Ca intake, leads to a considerable reduction in bone mineral density between the preterm birth and 38-40 weeks of post-conceptional age. These adaptive changes result in the so-called "osteopenia of prematurity", a common condition implying a higher risk of bone fragility and pathological fracture.

Although body mass gain rates may be higher in preterm babies receiving breast milk or formula, even when compared to intrauterine rates (16-22 g/Kg/d), when babies reach full term they usually have weight and length deficits[13;23;24]. Apart from this frequently insufficient linear growth, the reduced bone mineralization is an almost universal phenomenon, with variable degrees of severity ranging from a reduction in bone mineral density (a basically adaptive non-pathological phenomenon to prematurity) to apparent rickets with craniotabes and fractures. The term osteopenia is generally reserved for a decrease in bone mineralization while the term rickets is reserved to apparent disease, with typical metaphysial changes and/or pathological fractures. The osteopenia of prematurity seems to be an adaptive phenomenon which resolves spontaneously. At 6 months of corrected age, the bone mineral density adjusted for weight and length has reached normal values for comparable post-natal age term infants[6;22].

Recommendations for Ca and P Intake in Preterm Infants

The purpose of administering appropriate amounts of Ca and P is to make these two minerals fulfill their metabolic functions and, above all, to ensure adequate healthy bone formation. Insufficient intake of Ca and P may lead to inadequate mineralization of the osteoid matrix, the bone mineral content is reduced, bones are abnormally fragile and there may even be growth failure. These manifestations constitute the osteopenia of prematurity.

The recommendations for the intake of Ca and P in preterm infants have been based on the requirements necessary to achieve intrauterine accretion rates, i.e. approximate to Ca and P retention rates which would have occurred if the pregnancy hadn't been interrupted prematurely[6;12]. This leads to the administration of very high amounts of Ca and P that widely exceed those which can be administered in non-supplemented breast milk. Based on this idea, preterm formulas with a high proportion of Ca and P have been traditionally administered although absorption and retention rates are known to be suboptimal for calcium. This exaggerated administration of little absorbable calcium is not harmless: it is associated with urinary overexcretion (risk of renal calcification) and a reduction in fat absorption, hardening of feces and lengthening of the intestinal transit, all risk factors of necrotizing enterocolitis[6;19]. Babies are exposed to these risks often without reaching intrauterine Ca accretion rates[6].
Ca retention depends on the administered amount, the absorbed fraction, the energy nutritional intake, the endocrine balance (parathormone, calcitriol and calcitonin) and phosphate levels[6;15;19;22]. The enteral administration of similar amounts of Ca and P transported placentally does not guarantee a Ca retention similar to the retention in the fetus[6;17]. It is advisable to provide lower amounts of calcium which are better absorbed.

In fact it might necessarily not be appropriate to reach accretion levels similar to intrauterine levels. The skeletal adaptation to a preterm birth provides the newborn preterm infant with a lower amount of calcium than a fetus of comparable gestational age receives, which leads to good quality bone and appropriate structural resistance rather than just increasing bone mineral content[6;19;22].

Additionally, if lower but highly absorbable amounts of Ca and P are administered (e.g. breast milk + fortifier) bone mineral content may be maintained at a level high enough to prevent abnormal fragility and risk of fracture. However, some (tolerable) degree of osteopenia of prematurity cannot be avoided[12;19].

The evidence suggests that medium and long term bone quality (measured ultrasonographically and/or by DEXA) is equally adequate, regardless of whether Ca and P levels were administered in amounts to approximate the intrauterine accretion rate or the administration is only aimed at avoiding risky bone mineral content levels[6;19;25-31].

Whether the presence of mild to moderate and transitory osteopenia (rather than a deficiency disease it would be an adaptive reaction to the preterm birth) affects the final length attained by preterm infants or not is yet to be ascertained.[6]

Based on the evidence and these positions, for very low birthweight infants the recommendation of an intake of highly absorbable Ca 100-160 mg/Kg/d (e.g. breast milk plus fortifier) and P 60-75 mg/Kg/d, leading to a Ca retention of around 60-90 mg/Kg/d, a dose enough to prevent fractures and rickets of prematurity seems reasonable[6]. For infants close to full term, Ca and P deficits at birth are lower and the objective to control the risk of severe osteopenia and fractures may be attained with unmodified preterm breast milk. It also seems reasonable to recommend regular and prolonged mechanic skeletal stimulation to reduce modeling and increase mineralization[6;19].

2.2 Feeding and Nutrition Objectives and Goals for Preterm and/or Low Birthweight Infants.

Question: **What should be the purposes and goals of feeding in preterm and/or low birthweight infants?**

Evidence-based Answer: **Traditionally, it has been claimed that preterm babies should attain intrauterine somatic growth and growth goals and rates. The recognition of a process of adaptation in preterm infants with parameters and conditions that differ from the appropriate parameters and conditions for a fetus of the same gestational age has led to a reassessment of this paradigm by many investigators.**

The purpose of preterm infant feeding, if possible without exposing them to a higher risk of complications (e.g. necrotizing enterocolitis), is to get them as close as possible to the somatic growth targets they would have attained had they been born at term. This is often not possible or unwise during the transitional phase of adaptation to extrauterine life.

During the transitional phase, the nutritional deficits and the negative impact of adaptation on growth and body composition should be minimized; and during the stable growth period (stabilization after transition) efforts should be made at recovering adequate growth rates and, if possible, favoring catch-up growth.

At first it is more important to attain adequate weight, length and head circumference gains (e.g. 15g/kg/d of weight, 1 cm/weight in height or 0.7 cm/week in head circumference), than to reach specific weights or lengths according to pre-specified corrected ages (e.g. > 2500 g when reaching full term).

Evidence Level: **Experts' consensus, non-systematic reviews and papers about opinions by experts and scientific societies.**
Level of Consensus: **Unanimous**

Rationale:

Preterm newborn infants leave the intrauterine environment and the placental nutrient transfer prematurely. They do not complete nutrient, vitamin and mineral deposits as do term babies, and their body mass and size are smaller.

After birth, both term babies and preterm babies have to adapt to extrauterine life. There is a change in the way they acquire nutrients, in energy expenditure, use of reserves and development and mass accretion rates. This is a normal occurrence for term babies but may represent a very traumatic and dysfunctional phenomenon for preterm infants[6;32].

The traditional goal was the administration of nutrients as if the infant had stayed in the uterus, and efforts were made at successfully completing the interrupted gestation[5;7;33;34]. The extrauterine environment differs considerably and implies risks and limitations, which in many cases turns insisting on emulating placental nutrient transport into a barely realistic and risky attempt. In any case the best possible nutrition should be provided, though not at any cost.

A "permissive" under-nutrition process may be suggested, providing at least critical quantity and quality of essential nutrients indispensable to preserve the preterm infant's life and integrity during the transitional growth period[2;5].

Preterm newborn infants enter a transitional and immediate adaptation phase, where survival and maximal preservation of potentialities are a priority. In general, nutritional intake during this stage is significantly limited, and babies may be exposed to nutritional deficits or a worsening of them, and alterations in body composition.[2]

The infant enters the stable growth period after the transition and particularly when the gastrointestinal route may be used for nutritional intake[2;7]. This period is directed to recover from the loss of growth rate and normalize body composition. At first it is more important to attain adequate weight, length and head circumference gains (e.g. 15g/kg/d of weight, 1 cm/weight in height or 0.7 cm/week in head circumference), than to reach specific weights or lengths according to pre-specified corrected ages (e.g. > 2500 g when reaching full term).

The fetoplacental unit is highly efficient in nutrient transfer and retention for the fetus. The attempt to systematically emulate the placental function in preterm infants may not only fail to achieve intrauterine growth targets but also expose the baby to serious risks. For example, the administration of calcium in very low birthweight infants to ensure a bone mineral content equivalent to term infants requires very high levels of Ca and P, and this exposes the babies to a higher risk of enterocolitis[6;19;35]. These babies are going through a process of skeletal adaptation to preterm birth which, provided a minimum intake sufficient to avoid bone fragility, will lead them to an adequate bone mineral content in a few months[6;16;19;36].

3. ROLE OF BREAST MILK IN PRETERM AND/OR LOW BIRTH WEIGHT INFANT FEEDING DURING THE STABLE GROWTH PERIOD.

Breast milk is preferred because it is safer and more appropriate in terms of nutrient intake and immunological properties, but in some cases it may be insufficient to fulfill all the requirements for preterm babies.

The risk-benefit balance is delicate and should consider several factors. As St. T. Kempley et al.[7] state:

"Understanding the nutritional needs of the sick preterm infant will ensure that nutritionally adequate milks are used, but to minimize complications an understanding of the interaction between milk composition and neonatal gastrointestinal physiology is required. Unmodified preterm breast milk is probably the safest milk, but might require supplementation with fortifiers to meet nutritional needs. Fortification affects the osmolality, protein and mineral content of breast milk in ways that can have adverse effects on intestinal function. Although preterm formulas meet the nutritional requirements of sick preterm infants, formula milk is associated with an increased risk of necrotizing enterocolitis."
The characteristics of an ideal feeding strategy for the stable growth period include:

- The feed should satisfy nutritional requirements both in terms of nutrients and energy and quality of the substances received.
- The enteral route is available (preferably orally).
- Optimal absorption and intake of administered calories and nutrients.
- The feed should be adequately tolerated by the gastrointestinal tract of preterm or low birthweight infants.
- Risks associated to feeding should be minimized: necrotizing enterocolitis, intolerance, metabolic disorders, etc.
- There should be additional advantages: immunological, psychomotor development, etc.
- The strategy is widely and easily available and is cost-effective.

Breastfeeding (breast milk from the baby's mother, whether suckled or extracted and given orally or by gastroclysis) widely fulfils these requirements for term or close to term babies. It could not be a complete source of nutrients for more immature or malnourished infants whose requirements are higher for some nutrients, and breast milk fortification or supplementation should be considered in these cases. When breast milk is modified or fortified by adding nutrients and caloric density, advantages related to safety, tolerability, absorption and assimilation of some nutrients may be lost or reduced. However, many nutritional and immunological (generally lacking in commercial preparations) properties remain.

3.1 Preterm Breast Milk Composition and Requirements of Preterm and/or low Birthweight Infants

Question: **Does preterm breast milk fulfill the energy, macronutrient, Ca and P requirements for preterm or low birthweight infants during the stable growth period?**

Evidence-based Answer: **Milk composition in mothers of preterm babies differs from those of term babies. Higher sodium and protein levels in preterm milk are the most consistent differences. Preterm milk is richer in protein, even twice as much than term milk; besides, lactoserum (milk protein) provides not only the nine amino acids essential for humans but also taurine, glycine, leucine and cysteine, amino acids that are essential for preterm babies. These protein and nitrogen levels could be sufficient in many cases, but some preterm infants may require more protein than that they can obtain from preterm breast milk to keep up with the growth rates needed, especially for catch up growth.**

Fat contents, particularly medium and intermediate chain fatty acids, are higher in preterm milk although their concentration could fail to meet early requirements in many preterm infants. Nevertheless, the levels of long chain polyunsaturated fatty acids (arachydonic and docosahexaeonic) in preterm milk remain high for at least six months to more than twice as much in term milk, probably resulting in a better source for these fatty acids in preterm infants.

The amount of calories, calcium and phosphate in preterm milk is generally higher than in term milk. However, the calcium/phosphate ratio could not meet the increased needs of these minerals, especially in extremely low birthweight preterm infants.

Additionally, the preterm colostrum contains more IgA, lysozyme and lactoferrin, and higher counts for total cells, macrophages, lymphocytes and neutrophils.

When babies enter the stable growth period, particularly after they have reached a weight of 1500 g, it is possible to maintain adequate growth rates (15-20 g/Kg/d) with exclusive unmodified breastfeeding by their own mother. In case of failure to reach this growth rate, fortification or supplementation or its continuation, if already established, should be considered.

Appropriate fat-soluble vitamin (A, D and K) supplementation is necessary.

Evidence Level: **longitudinal and cross-sectional descriptive studies. Narrative reviews. Experts' consensus.**

Level of Consensus: **Unanimous**

Rationale:

A study on preterm milk maturation from mothers giving birth at different gestational ages[13] found that protein levels were initially high and then steadily decreased as infants approached full term. Protein concentration was inversely proportional both in the post-natal and the post-conceptional ages. During milk maturation lactose concentration remained unchanged. Calcium and phosphate concentrations were higher than in term milk, and remained stable at least until full term, in a 2:1 ratio. Chemical analyses of preterm breast milk at the beginning and at the end of each feed (foremilk and hind milk) showed some homogeneity in all nutrients except fat. Regardless of the gestational age and milk maturation (time elapsed since the preterm birth), hind milk is considerably richer in fat and caloric density.

The results from this study are consistent with the literature both for high-income countries [37-41] and for preterm composition in medium and low-income countries[42-44]

In the two to three first weeks of post-natal life, protein concentrations decrease significantly until reaching the usual levels in mature (term) milk. This fall in concentration seems to occur early and quickly, and it might be insufficient to fulfill increased protein requirements in infants born prior to week 32-34 during the weeks before they reach 38-40 weeks of gestational age[13].

Serum protein not only contains the nine essential amino acids but also taurine, glycine, leucine and cysteine, which are considered essential for preterm babies, i.e. they represent the most qualitatively adequate protein source, even when it may be quantitatively insufficient in some cases.

Both total fat and medium and intermediate chain fatty acid contents are higher in preterm milk. However, given the increased energy requirements even these higher concentrations might not be enough to meet early requirements, particularly among smaller preterm infants[45]. Nevertheless, at least one study shows that the levels of long chain polyunsaturated fatty acids (arachydonic and docosahexaeonic) in preterm milk remain considerably high for at least the first six months of post-natal age, to more than twice as much in term milk. Thus in preterm babies breastfeeding with preterm milk from their own mothers could represent an adequate source of these essential fatty acids[46]

Fat digestion is quick and easy when infants receive fresh untreated milk from their mothers. The manipulation of extracted milk may interfere with an adequate fat intake. For example, adding calcium may precipitate lipids, and sterilization may reduce lipase activity[15;47;48]

Unmodified breast milk is unable to provide the Ca and P intake which many preterm infants (particularly extremely low birthweight infants) require to maintain mineral accretion rates similar to intrauterine rates[6;7;19;22;35]. There should be admitted that there is a process of bone adaptation to the preterm birth in these infants, leading to some degree of osteopenia; the nutritional goal should be preventing symptomatic osteopenia (rickets). Chan et al. [30] report a randomized trial involving 59 preterm infants of less than 1500 participants who received the intervention and were followed for 16 weeks. The 16 participants allocated to unmodified breast milk had lower short-term bone mineralization and length gain rates, with higher alkaline phosphatase levels.

The evidence suggests that the best way to administer easily absorbable Ca and P is by fortifying breast milk (preferably milk from the same mother), since both absorption and assimilation (incorporation to the bone) are more efficient and safer than preterm formulas[6;19;34] and enough amounts of Ca and P are given to ensure an adequate quality bone (avoiding the risk of fracture) even when bone mineral content may be lower.

Besides, there is no consistent evidence supporting the use of systematic calcium and phosphate supplementation as a strategy to improve long term bone mineralization in infants > 1500 g at birth. The report of a randomized trial [31] indicates that infants 1800 g receiving breast milk with no Ca and P supplementation develop hypophosphatemia and lower growth rates in the medium and short term. Fifteen of the 71 patients allocated (20% of the recruited sample) completed the study, and this hinders the validy of the study findings. The remaining studies[26;27;49-51] (randomized controlled trials and analytical cohorts) agree that no effects of the Ca and P supplementation are found in medium- and long-term bone mineralization and quality for preterm infants with no serious symptomatic osteopenia (e.g. fractures, craniotabes). What's more, Bishop[50] y Morley[51] (apparently in two reports of the same cohort) suggest that the quality of bone mineralization between the ages of 5 and 9 is inversely proportional to the amount of breast milk received by preterm infants in their first year of life.

Fat-soluble vitamin supplementation of preterm nutrition during the stable growth phase should be administered regardless of whether the kangaroo feeding and nutrition strategy is used or not. Therefore this is not discussed in these guides. Special emphasis should be placed on the need of appropriate vitamin K supplementation. If interested in this issue, please refer to the appendixes where a review of the rationale and use of Vitamin K (repeated administration weekly until full term) for preventing the hemorrhagic disease of the preterm infant, including the late type, is described.

3.2 Advantages of Breastfeeding for Preterm and Low Birthweight Infants During the Stable Growth Period.

<u>Question:</u> Is there any evidence that breastfeeding reduces the risk of NEC in preterm and/or low birthweight infants?

<u>Evidence-based Answer:</u> **Yes. Despite the weak, observational methodology, the clinical evidence corpus and the patophysiological rationale indicate that non-fortified breast milk reduces the risk of necrotizing enterocolitis (NEC) when compared to breast milk plus formula supplementation, and this is a safer strategy than exclusive formula administration. There are no adequate data on the risk or safety of fortified breast milk.**

<u>Evidence Level:</u> prospective and retrospective comparative observational studies, experts' consensus.

Level of Consensus: **unanimous**

Rationale:

One of the reasons for recommending preterm infant feeding based on breast milk from their own mothers is the observation that breast milk administration is associated with a decreased risk of NEC. The main risk factors for NEC are formula feeding, hypoxia/ischemia, bacterial infection and prematurity. More than one of these potential etiological factors are often found among many of the newborn infants with NEC. The exact protective mechanism of breastfeeding against NEC is unknown but it may be related to the presence of antimicrobial agents in breast milk, with differences in bacterial colonization of the gastrointestinal tract in breastfed infants or with the existence of acetylhydrolase in breast milk, an enzyme which degrades the platelet activating factor (PAF), implied in the pathogenesis of necrotizing enterocolitis.

The role of non-fortified breast milk in the protection against NEC is assessed in three meta-analyses: formula vs. preterm breast milk[52], formula vs. term breast milk[53] and formula vs. donor's breast milk[54].

As to preterm milk and formula, only one small clinical trial was found on preterm breast milk from the same mothers, which did not show any difference in the incidence of NEC although it suggested a higher frequency of intolerance in babies receiving formula.

Six studies were included in the review on term milk, none of which studied fortified breast milk. This review did not find enough data on the incidence of NEC to assess the frequency of this outcome.

As to donor's (pasteurized) breast milk, four small studies were found in the meta-analysis. A three to four times lower risk of NEC is evidenced among infants receiving breast milk according to the meta-analysis data. Of note is the fact that these four studies were included in the previous meta-analysis (term milk vs. formula) which could not assess the NEC outcome.

The study by Lucas[55] reported the highest number of subjects, including 51 clinical cases of NEC in 926 preterm infants receiving three types of feeds: a) breast milk (from the same mother or donor) alone, b) breast milk plus formula and c) formula alone. The estimated risk, after adjusting for differences in known risk factors of NEC, resulted in 6 to 10 times higher in formula-fed infants versus exclusive breastfeeding (from the same mother and/or donor).

Question: **Is there any evidence that breastfeeding reduces the risk of diarrheal disease in preterm and/or low birthweight infants?**

Evidence-based Answer: **Observational studies show that breastfeeding may reduce the risk of diarrheal disease both in term and preterm infants.**

Evidence Level: **comparative observational studies.**

Level of Consensus: **unanimous**

Rationale:

Seven studies were found in the literature search, of which 6 were observational and 1 experimental. A reduction in the number of Diarrheal Disease (DD) was found during the follow-up in all the studies except one.

The study by Duffy et al. [56] (prospective cohort) included 197 mother-child dyads, followed for 6 to 9 months during the rotavirus season. Data were collected by telephone or personal interview, and coproscopic investigations at 24 hours from the diarrheal episode. Feeding was classified into exclusive breastfeeding, mixed feeding and formula feeding. The outcome measures were the number of stools and the presence of vomiting. Presence of rotavirus was another outcome measure. Results showed that the incidence of DD is reduced (70%) in the exclusive breastfeeding group for a period of more than 4 months. Rotavirus infections were less severe in breastfed infants. After adjustments for the baby's sex and ethnicity, and mother's age, schooling, occupation and marital status, BF showed a protective effect (RR 0,29 95% CI 0,24-0,83)

The study by Howie et al.[57] (prospective cohort) included 674 mother-child dyads, 618 followed for 2 years and 545 examined at the age of 7[58]. Data were gathered by interviews at pre-specified ages and a retrospective study of case histories. Feeding was classified into 1) predominantly non-supplemented breastfeeding, only water and fruit juice 2) mixed feeding for 13+ weeks 3) breastfeeding discontinued before 13 weeks and 4) no breastfeeding. There was a positive effect on the incidence of DD: a 25% reduction was found among breastfed babies versus the no feeding group. This effect persisted all throughout the first year of life. Frequency of hospitalization due to DD was lower among babies receiving only breast milk for more than 13 weeks versus those who were never breastfed. Results were adjusted considering social and economic factors.

In the study by Rubin et al.[59] (prospective cohort) involving 500 infants, 461 were followed during the first month of life and only 233 at 12 months (44% of the sample). Information on feeding type (whether breastfeeding was included) and diarrheal disease episodes was collected using mailed questionnaires. This study did not find any difference between the groups after adjusting for confounding factors. No negative effect of breastfeeding was found.

The study by Dewey et al.[60] (prospective cohort) followed 87 infants, 46 breastfed y 41 non-breastfed. Data were collected using a weekly telephone or personal interview with the mother until 24 months and a daily report by the mother on disease symptoms. Feeding was classified into two groups: 1) occasional feeding using a baby bottle, 2) occasional breastfeeding. None of the infants received solid food before 4 months. A positive effect with breastfeeding was found, after adjusting for confounding factors, and the incidence was twice lower in the breastfeeding group.

The study by Scariati et al. 1997 (ID 443) (prospective cohort) included 1743 subjects. Data were collected using a series of 11 questionnaires sent by mail since the second trimester of pregnancy until the end of the first year. Feeding was classified into 5 groups 1) exclusive breastfeeding (BF), 2) high mixed feeding: (BF 89-99%) 3) medium mixed feeding (BF 58-88%) 4) low mixed feeding (BF 1-57%) and 5) exclusive formula. DD and the risk of diarrhea as number of infants with DD according to feeding in the previous month were defined. After adjusting for confounding factors, the risk of DD was 80% higher in the non-breastfed group and an apparent dose response effect was found: the lower the amount of BM, the higher the risk of DD.

The study by Kramer et al.[61] (randomized trial about promoting breastfeeding, with a prospective cohort in the trial) included 17,046 mother-child dyads, 31 healthcare centers randomized to the breastfeeding promotion intervention (16) and no intervention (15). Follow-up at 12 months of age was possible in 16,491 pairs (96.7%). Follow-up consisted of medical visits every month or when babies were sick; relevant data were compiled in those visits. The "Baby-Friendly Hospital Initiative" was implemented in 16 healthcare centers, and at 1 year exclusive breastfeeding was 43.3% in intervention centers, 6.4% in control centers. Six months later, the difference was 7.9% versus 0.6%. A positive effect was found in favor of breastfeeding: the risk of DD in intervention centers was 40% lower than control centers; besides, the incidence of DD between 3 and 6 months in exclusively breastfed infants was reduced by 65% in exclusive breastfeeding infants until 6 months in relation to the incidence of breastfed infants until 3 months.
The study by Beaudry et al.[62] (6-month historical cohort) included 776 pairs (62% of eligible mothers accepted the invitation to participate, and of these 91% reported useful data). Data were collected using a standardized form sent to mothers a week before the baby's 6 months of age, which requests information on feeding mode and diseases including the age in weeks when another milk or solid food or liquids were started. Babies were classified weekly as breastfed (exclusive breastfeeding or not, since birth till weaning) and non-breastfed. After adjusting for confounding factors a positive effect was found in favor of BM: 47% reduction in global incidence during the breastfeeding weeks versus non-breastfeeding weeks: RDI 0.53; 95% CI 0.27-1.04

Question: **Is there any evidence that breastfeeding reduces the risk of low respiratory tract infection during infancy in preterm and/or low birthweight infants?**

Evidence-based Answer: **A meta-analysis of observational studies including term and preterm infants shows that exclusive breastfeeding reduces the risk of hospitalization due to serious respiratory tract infection during infancy by at least 4 months.**

Evidence Level: **meta-analyses of comparative observational studies.**

Level of Consensus: **unanimous**

Rationale:

Low respiratory tract infection is very common in the first year of life. The incidence and the severity are higher in preterm babies[63]. Breast milk contains immunological factors that could protect both against frequency and severity of infections.

A meta-analysis of observational studies was found in the literature search[64], which found 33 studies, of which nine were included in the effect estimate; these nine studies properly defined breastfeeding (type and duration) and estimated frequency of infection using validated methods. The effect of exclusive breastfeeding was compared for at least 4 months versus no breastfeeding as to frequency and severity of the hospitalization due to acute respiratory tract infection. Of the 4525 studied infants there is no information as to proportion of term and preterm babies. There is no uniformity as to the length of follow-up (about 1 year of age) either. The main finding was a reduction of up to 57% in the risk of hospitalization due to respiratory tract infection (RR 0.43 95% CI 0.22-0.85) in breastfed infants, even after controlling for confounding factors such as home exposure to smoking and socio-economic level.

Question: **Is there any evidence that the breastfeeding is associated to better neurological and psychomotor development and academic performance/intelligence in preterm and/or low birthweight infants?**

Evidence-based Answer: **It is unclear whether there is an association between breastfeeding and better neurological, psychomotor development and better academic performance. Instead, an association between breastfeeding (the mother decides to breastfeed her baby) and better neurological and psychomotor development and intelligence has been confirmed. Overall the documented effects are more significant in preterm infants than in term infants.**

Running experimental studies on humans allocating subjects to breastfeeding or formula is ethically inappropriate. Most of the available observational studies show a positive association between breastfeeding and better cognitive development. Attributing these effects to human milk's nutritive and biological properties is difficult, since breastfeeding in all those studies is associated in not only to breastfeeding (by the same mother) but also to various levels of mother/baby interaction (related to the breastfeeding act), more encouraging and devoted mothers (who have voluntarily decided to breastfeed). In fact, various studies and systematic reviews suggest that the positive effects of breastfeeding may be attributed to confounding factors instead of a net effect of breast's milk. In any case, the evidence shows it is appropriate to encourage breastfeeding as much as possible since the point of view of the neurological and intellectual development.
Evidence Level: **comparative observational studies and meta-analysis of observational studies.**

Level of Consensus: **unanimous**

Rationale:

Very long chain polyunsaturated fatty acids, contained in human milk, are incorporated in neuron cell membranes. The evidence suggests a positive correlation between docohexanoic and arachydonic levels and Bayley scale mental and psychomotor development scores[65]

Apart from breast milk chemical properties, breastfeeding improves and strengthens mother/baby bondin[66], which may stimulate the baby's intellectual development.

The evidence supporting the superiority of breast's milk is based on observational studies mostly consisting in post-hoc sub-analyses of controlled trials aimed at answering other questions. The identified systematic reviews summarizing results of these studies found that, despite methodological flaws, all suggest that the administration of breast milk is associated with medium and long-term better intellectual development as compared to using formula milk, and these differences are more evident among preterm infants than term infants.

Attributing these effects to human milk per se or to other related circumstances surrounding the decision to breastfeed (affective bonding, mother's educational level, socio-economic level, etc.) is difficult. In fact, some studies and systematic reviews suggest that almost all of the observed beneficial effects in development and intelligence in breastfed infants may be accounted for by associated protective factors, and the net effect related to human milk is marginal. Instead, it can be ascertained that breastfed infants have better opportunities of intellectual and psychomotor development.

There is a widespread and emotionally charged debate surrounding these issues, since promoting breastfeeding is not only part of a scientific but also political and ideological agenda in many national, regional and international organizations (WHO, UNICEF), etc. A detailed review of consulted and examined observational studies and systematic reviews is included in the appendix at the end of the present document. The main source of evidence consulted is the chapter on infant feeding mode and child development from the book "Biologie de l'allaitement de M.Beaudry, S.Chiasson, J.Lauziere, 2006, Presse de L Universite du Québec"

Question: **Is there any evidence that breast milk administration is more beneficial for preterm and/or low birthweight infant nutrition?**
Evidence-based Answer: **Yes. Both term and preterm infants receiving breast milk have a lower basal energy intake, associated to more efficient nutrient absorption and use.**
Evidence Level: **observational studies and a randomized controlled trial**
Level of Consensus: **unanimous**

Rationale
A published review of observational studies and the results from a crossover randomized trial[67] show that energy intake measured by indirect calorimetry is lower in infants receiving breast milk than those receiving formula (both term and preterm infants). These differences become more significant when adjusting for dietary caloric intake. This higher efficiency is attributed to easier nutrient digestion and absorption and to better balanced amounts of the different energy sources in breast milk.

4. ALTERNATIVE STRATEGIES TO UNMODIFIED BREAST MILK

Question: **When breastfeeding is insufficient to meet the requirements, which are the feeding strategies for preterm and/or low birthweight infants in the stable growth period?**

Evidence-based Answer: **According to the nutritional source, feeding strategies for this period include:**

- **Feeding based on breast milk from the same mother + vitamins A, D, E and K:**
  - **Exclusive, unfortified, unsupplemented.**
  - **Fortified (fortifiers added to extracted milk)**
  - **Preterm milk supplementation,**
  - **Donor's (preterm or term) pasteurized and fortified breast milk supplementation**
- **Feeding based on special preterm formula**
- **Exclusive or supplementary use of other sources of oral or enteral nutrition: protein hydrolysates, element and semi-element preparations, etc.**

The preferred mode of administration is breast milk from the same mother, directly from the breast or by using strategies which minimize energy intake and maximize caloric density (by time, hind milk technique (see appendix), etc.), and supplemented if required (suboptimal growth rates) using fortification or preterm formula. Any food other than direct breast milk should be administered using appropriate methods to preserve an adequate suction of the nipple and to favor breastfeeding: avoid the use of baby bottles or rubber teats.

Evidence Level: **narrative and semi-systematic reviews, experts' consensus**

Level of Consensus: **unanimous**

Rationale: Not applicable.

5. KANGAROO MOTHER CARE METHOD AND SUCCESSFUL BREASTFEEDING

Question: **Does the Kangaroo Mother Care Method prompt a successful breastfeeding in preterm and/or low birthweight infants?**

Evidence-based Answer: **Yes. For both term and preterm infants the evidence indicates that the Kangaroo Position results in successful breastfeeding and increases the number of breastfeeding mothers and breastfeeding duration. The mechanisms involve the biological effects of skin-to-skin contact as well as behavioral and emotional factors: there is a reduction in the time mother and baby spend away from each other, and the health care staff stimulates breastfeeding, trains mothers appropriately and provides efficient support during the process while mothers improving bonding thanks to the Kangaroo Position may feel more predisposition to breastfeed, which in turn improves bonding quality.**

Evidence Level: **controlled randomized trials, trial meta-analyses**

Level of Consensus: **unanimous**

Rationale:

Initiating and maintaining breastfeeding is a normal biological event. Hormonal, neurological, emotional and behavioral factors are involved. There is evidence[68] indicating that early skin-to-skin contact in term infants stimulates the initiation of a successful breastfeeding and also has an impact on the number of breastfeeding mothers and breastfeeding duration.

Initiating and maintaining breastfeeding in sick or preterm infants do not occur spontaneously. The baby may be weak or immature to suck, and mother and baby are often separated early and for long periods to provide the baby with the care he/she requires during the transitional phase.

The Kangaroo Mother Care Method aims at initiating mother/baby contact as soon as it is safe and possible and then move on to the quickest rate possible in the adaptation of the mother-child dyad to the Kangaroo Position. This leads to a shorter period of separation for mother and baby and to initiating skin-to-skin physical contact, which helps in the initiation and organization of the mechanisms involved in milk production and let-down. As part of the adaptation process, the kangaroo team healthcare staff also implements techniques to preserve breastfeeding, such as mother's milk and colostrum collection, and administration to the baby until direct suction is established. All these processes favor initiation and maintenance of a successful breastfeeding. The net effect is seen in the higher number of breastfeeding mothers, and a longer duration of breastfeeding in mother-child dyads exposed to the kangaroo mother method. This is supported by scientific evidence, both for the intermittent skin-to-skin contact provided in the neonatal unit to preterm babies with varying degrees of stability (during the transitional or stable growth periods) [69-73] or the continuous, prolonged Kangaroo Mother Care Method during hospitalization, for example rooming-in mother and baby in the Kangaroo Position[74;75] or continuing the Kangaroo Position after discharge[76;77]

6. PRACTICAL RECOMMENDATIONS ON KANGAROO FEEDING STRATEGY AND NUTRITION

6.1 Target Population

Preterm or Low Birthweight Infants

Kangaroo feeding recommendations are addressed to all preterm and/or low birthweight infants (<2500g), hospitalized or at home, who have initiated the adaptation to the Kangaroo Position.

The Kangaroo Mother Intervention is provided to preterm and/or low birthweight infants as soon as possible and

only if the baby can tolerate it and meet criteria such as: vital signs are stable, no bradycardia or desaturation is observed while the baby is manipulated, and there is no primary apnea or, if previously present, it has already been controlled.

The recommendations are primarily addressed to babies during the stable growth period but oral feeding with extracted milk may (or should) have been initiated at some time during the transitional phase, as part of the initiation and implementation of the oral route in these infants.

Feeding strategies during the transitional period are out of the scope of these guides.

Even when the (gradual, intermittent or continuous) Kangaroo Position may be initiated during the transitional period, the feeding modes during the transitional period would be included later. During the stable growth period of these infants with a reasonable clinical stability and tolerability to enteral –preferably oral- feeding, the main feeding objectives are a) recovery of growth until reaching a body size adequate for the corrected age and b) normalization of body composition.

A kangaroo feeding scheme is recommended during the hospitalization prior to discharge, which typically occurs in preterm infants going 33-34 weeks of post-conceptional age, followed by a feeding scheme for the kangaroo follow-up period until the baby reaches the 40 weeks of post-conceptional age.

6.2 Feeding Routes

6.2.1 Gavage:

Breast milk may be administered by intermittent gastroclysis (gavage) in immature infants in which the suction reflex and adequate suction/swallowing coordination is absent due to prematurity or neurological disorders or malformations, but in which nutrients may be absorbed through the intestine. Suction stimulation is initiated as the baby is fed via gavage (non-nutritious suction, an important phase to stimulate suction maturation).

6.2.2 Oral Route by Suction

The fetus may purse the lips at week 20; the suction reflex is present as from week 24 and turns more vigorous as from week 32. All previous activities are a basic preparation stage before week 32-33, when the baby can synchronize suction and swallowing and may be fed orally directly by suction.

6.2.3 Mixed Routes

Daily weight gain is monitored in the preterm baby fed by tube and receiving non-nutritious suction stimulation periods. With the support by the kangaroo clinical team, the baby is exposed to the breast when weight is stable or there has been a gain for more than two days and the oral route is possible in 50%-70% of the total daily volume, despite the required suction activity and the energy expenditure.

Once the baby can suck from the mother's breast adequately, a good coordination between regular weight gain and volume received by gavage of about 100 ml/Kg/d for a few days is expected to withdraw the tube and leave the baby with exclusively direct breast milk.

6.2.4 Oral Route by Giving Drinks or Drip

In case of mother's absence, the oral feed is given as a drink or by drip. The use of baby bottles or rubber teats should be avoided since it is mistaken by the nipple. When using baby bottles or teats, the quality of suction from the mother's nipple becomes inadequate and the volume of breast milk may be reduced as a result of inefficacious suction. The evidence shows that feeds may be administered using a glass without further delay, when trained staff is in charge78;79.

However, feeding using a container should not be administered for too long without proper suction stimulation as it delays the establishment of coordination between suction and swallowing.

6.3 Suction Stimulation

The moment to start suction stimulation and the suction administration mode is controversial.

The process recommended in these guides for the stimulation of suction is described as follows:

When the mother holds her baby in the Kangaroo Position, the moments during which the baby is alert are used to apply the so-called non-nutritious suction. The baby usually has a nasogastric or oral feeding tube. The aim of non-nutritious suction is to establish the coordination among suction, breathing and swallowing. Early training may foster a quicker maturation of suction skills in more immature preterm infants (29-32 weeks).
While using gavage, the nipple or a gloved finger is introduced in the kangaroo baby's mouth; the finger should be moistened in milk, and every three to four suctions it is removed to enable the breathing pause. At the beginning the number of suctions is minimal to avoid exhausting the baby, resulting gradually in a pattern of eight to ten suctions and a spontaneous breathing pause. This way quality and maturation of suction are assessed: suction/breathing/swallowing coordination, oral motor system, breathing pattern, absence of fatigue or stress signs.

This suction training is better achieved if the mother's nipples are used, and this training is comforting for both the baby and the mother

Daily weight gain is monitored. An extremely fast training is not useful, in spite of a successful suction and suction/swallowing coordination; some infants lose weight when engaged in the suction activity.
Once the baby can suck from the mother's breast adequately, the coordination is adequate, the volume received by gavage is about 100 ml/Kg/d for a few days, and weight is maintained or more is gained, the tube is withdrawn leaving the baby with directly sucked breast milk alone.

6.4 Mode of Administration by Suction

Absence of mothers in neonatal units and the need to feed the baby by suction fostered the use of baby bottles or teats. This type of suction differs greatly from the suction straight from the breast, and interferes with adequate suction stimuli making the baby suck adequately from the nipple and favoring appropriate milk production. The absence of the mother for longer periods together with the use of baby bottles or teats are the major reasons for failure in breastfeeding among these fragile baby, who require more milk from their mothers.

The trials where milk is administered using a cup, a glass or syringe show that, given the proper training, these techniques do not take more time and result in a better adaptation of tube feeding to direct breast suction. However, prolonged feeding using a container without appropriate suction stimulation may also be inconvenient since it delays the maturation of suction/swallowing coordination.

The ideal mode of administration is passing from enteral feeding by a tube directly to breastfeeding by direct suction and intercalating feeds using a glass or cup in case of mother's absence.

6.5 Nutrition Source

6.5.1 Colostrum

For hospitalized preterm babies without oral feeding, their own mothers' colostrum will be administered as soon as possible, using a tube, as trophic stimulation of the intestine and in turn stimulation of immunological protection and maturation, rather than nutritional intake.

6.5.2 Exclusive, Breast Milk from the Same Mother.

In infants <1500g enteral feeding will be initiated preferably with exclusive breastfeeding plus parenteral nutrition. Doses are small at first and then they are gradually increased according to tolerance. When the dose is about 100ml/kg/d (according to protocols in each neonatal unit) or a week has elapsed, fortification should be started, if the baby's status allows it, for better calcium, phosphate and protein intake.

For newborn infants >1500g that can suck from their mothers' breast, exclusive breastfeeding is the best mode with a careful monitoring of weight gain, during hospitalization or kangaroo follow-up. If these babies are gaining weight while receiving milk by direct suction, they are theoretically of 32 weeks of post-conceptional age and show a mature suction pattern. When adequate growth is not attained after considering the normal period of physiological weight loss (growth estimated as 15g/Kg/d in weight and 0.7 cm/week in length), the first option should be using hind milk from the same mother to provide supplementary caloric intake before considering

breast milk supplementation. Only when hind milk has failed, breastfeeding supplementation or fortification will be considered13 apart from a deep psychological support.

6.5.3 Fortified Breast Milk from the Same Mother

Fortified breast milk is indicated for infants <1500g at birth. There is no consensus as to the exact moment to initiate fortification but it should be implemented when the baby receives a volume of about 100ml/Kg/d to ensure intestinal tolerance47. Nevertheless, fortification is implemented when the baby is more than one week old and does not reach this volume.

Although no consensus has been reached either on time to discontinue fortification, it is applicable when the immature baby passes from the tube through which he/she receives fortified breast milk to exclusive breastfeeding by direct mother's breast suction, which generally occurs after week 32 and with weights of at least 1500g. At this point, fortification is discontinued to avoid interfering with breastfeeding, and daily weight gain is monitored.

6.5.4 Supplemented Breast Milk from the Same Mother

For hospitalized infants, when the mother is not present or the amount of milk she left is insufficient, breast milk supplementation is used to satisfy their requirements.
For most nutrients, there appears to be no difference between donor's fortified milk supplementation and preterm formula supplementation, except for Ca absorption, which is more complete in fortified breast milk than in preterm formula.

By contrast, there are differences when non-fortified donor's milk or formula supplementation is used.

6.5.5 Fortified Donor's Breast Milk

To be able to collect and fortify donor's milk, a breast pumping room with staff trained in milk extraction and conservation and for the freezing of milk from the same mother and pasteurization of donor's milk is necessary to avoid risks of contamination or transmission of infectious agents.

If these conditions are present, fortified donor's milk adequately administered (without baby bottles and teats) is the most appropriate milk after fresh breast milk from the same mother.

6.5.6 Preterm Formula

Preterm formula milk is used when breast milk is insufficient, there is no donor's milk bank and the baby is <1500g.

It is also used in the ambulatory follow-up program when a kangaroo baby does not grow adequately with exclusive breastfeeding or hind milk, and the suggested intense psychological support has been already applied. Fortified breast milk is an alternative but it may need to be manipulated, which makes its home use difficult and risky when hygiene cannot be ensured (risk of infection increases). For this reason the use of preterm formula is recommended in ambulatory environments. The liquid preparation, available in adequate dose vials, is preferable to avoid contamination, preparation errors and abuse. At first breast milk is supplemented with a volume of formula milk corresponding to 30% of the estimated daily serving for the baby. This supplement is distributed along the 24 hours of the day and is administered using an adequate method (without a baby bottle or teat) before each breastfeeding session. Once the baby attains adequate growth, this supplement is reduced gradually until discontinuation, if possible before full term.

6.6 Vitamins, Minerals and Trace Minerals

Calcium and phosphate should be administered in infants <1500g, ideally as fortification of breast milk from the same mother. The urinary excretion of calcium should be lower than 6mg/Kg/d and of phosphate higher than 4mg/Kg/d.

Vitamin physiological reserves are stored during the last trimester of pregnancy and breast milk falls short to provide an adequate intake, particularly as to fat-soluble vitamins. Vitamin supplementation is given in hospital and then as an ambulatory program until the baby reaches full term.

Vitamin D intake is recommended in about 400-600 IU/d; however, this depends on the amount of vitamin D contained in breast milk. For mothers with little exposure to the sun for long periods (winter through several months) it is advisable to give a higher dose to avoid rickets.

Vitamin A supplementation implies a dose of 1500-2500 IU/d and vitamin E 25 IU/d.
Vitamin K administration is more controversial, not so much regarding the administration of the first dose at birth but rather the repeated doses, particularly in infants receiving exclusive breastfeeding or with liver immaturity. In northern countries, vitamin K is given weekly until the baby initiates a supplementary diet. The Kangaroo Mother Program recommends the administration of Vitamin K 2 mg weekly and orally until the baby reaches the 40 weeks of post-conceptional age. In cases of navel bleeding, 1 mg is given intramuscularly.

6.7 Summary of Important Practical Aspects

For a successful breastfeeding, not separating the baby from his/her mother should be the rule. In the case of neonatal unit admission, times should be open day and night and the mother should be allowed to stay 24 hours with her baby.

Preterm babies at 32+ weeks, who have been born stable, should be placed together with their mothers in the first half an hour after birth to stimulate milk production and suction.

If the preterm baby is admitted and does not receive oral feeding, his/her mother's colostrum should be given as soon as possible, by a tube, as a trophic stimulation of the intestine.

Breast milk is still the ideal mode of feeding for preterm babies but might not contain the necessary intakes of calories and minerals in lower weight infants (<1500g). In this case, fortified breast milk is the most adequate and most tolerated mode of feeding to be given by tube to the preterm baby when he/she receives oral feeding. Non-nutritious suction is initiated as a preparation to direct breast suction and to suction/swallowing coordination. When the volume of fortified breast milk is higher than 100 ml/Kg/d and weight increases, the tube is withdrawn leaving the baby to direct breast suction from his/her mother.

If fortification is not possible (no fortifiers available as in Colombia, or absence of a breast pumping room where mother's milk may be fortified), the fortification technique using liquid preterm milk is an alternative but should be given using a container with a small amount, distributed along the 24 hours to avoid interfering with breastfeeding and to improve tolerance.

The Kangaroo Position stimulates breast milk production and should be initiated as soon as the baby stabilizes and for as long as the baby and his/her mother can tolerate.

Every neonatal unit should have a breast pumping room where mothers can extract their milk manually.

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EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR AN OPTIMAL USE OF THE KANGAROO MOTHER METHOD

IN PRETERM AND/OR LOW BIRTHWEIGHT INFANTS.

Evidence-based Answers

EARLY DISCHARGE AND KANGAROO FOLLOW-UP

Fundación Canguro and
Department of Clinical Epidemiology and Biostatistics
School of Medicine - Pontificia Universidad Javeriana

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Contents

1. EARLY DISCHARGE IN THE KANGAROO POSITION

1.1 "Early" hospital discharge

Question: **Is it safe and appropriate for stable preterm babies, regulating their temperature, to be discharged regardless of their weight?**

Evidence-based Answer: **The evidence suggests that there is no higher risk for preterm infants who are discharged regardless of their weight and gestational age if they regulate their temperature adequately and receive care from their mothers once they can feed and look after them.**

Evidence Level: **RCTs of variable quality and with different definitions for early discharge, experts' opinions**

Level of Consensus: unanimous

Rationale:

Data as the ones found by Orstenstrand et al.[1] allow a more informed evaluation of the balance between the risks and the cost-benefit relation of early discharge versus waiting until the baby reaches the pre-specified weight and/or gestational age. The authors show that in rich countries with easy access to the best neonatal care, a more liberal policy of discharge for preterm infants (35.7 weeks of post-conceptional age) does not lead to additional problems or risks for infant health and well-being. On the contrary, this helps foster parents' self-esteem and a feeling of competence in looking after their baby. These effects seem to persist at least for one year and could be relevant for the quality and strength of the mother/child relationship, already weakened by the initial and prolonged separation usually associated with prematurity.

The debate about the mother/baby relationship started in the 1970s, when Fanaroff, Klaus and Kennell reported increased risks of abuse and dropout in preterm infants especially with prolonged mother/child separation mostly associated with prolonged neonatal hospital stay[2-4]. These reports are particularly credible when we consider that parents are forced to see their baby in an incubator, connected to different tubes and machines that are not explained to them, and they are able to establish very little physical contact with their child or even none at all. For the mother, the baby looks very different from the image she has made of her baby, and little by little she starts feeling and thinking of him/her as a stranger.

Additionally, these parents become stressed and more prone to suffer from anxiety and depressive disorders than parents of term babies, after discharge (references). This obviously hinders even more the mother/baby relationship[5-8]

Early discharge regardless of weight, once the child regulates its temperature, has been evaluated in several studies. Shapiro[9] selects a low birthweight NB population with respiratory and hemodymanic stability; early discharge is randomly allocated when they regulate their temperature in the cot versus discharge at 2300 g. Both groups receive complete feeding orally. This study found that patients with early discharge did not show differences in morbidity and mortality or in frequency of hospitalizations during the follow-up to 1 year of corrected age.

Similarly, in the study by Brooten [10] infants <1500g are randomly divided into two groups: a) early discharge once the baby regulates temperature and b) discharge at 2200 g. The outcomes of this study are length of stay, age and weight at discharge, mortality, re-hospitalization, and severe illness. Early discharge NB were discharged earlier than babies in the control group, with no differences in the variables followed up to 18 months, and there was also a reduction in health care costs in the first 18 months

The study by Gunn et al[11] showed that once preterm infants regulate their temperature they can be taken home even before the weight gain phase. There was no additional morbidity or unfavorable effects on the duration of breastfeeding.

1.2 Hospital Discharge While in the Kangaroo Position

Question: **Is it safe and appropriate for a stable preterm baby not regulating their temperature spontaneously, but who does so while in the Kangaroo Position, to be discharged regardless of their weight or gestational age?**

Evidence-based Answer: **There is convincing evidence that low birth weight NB in KMCM can be discharged from the hospital while still in the Kangaroo Position, and that they can be discharged at smaller ages and weights than low birth weight NB in incubators, with no increased risks. In addition, early discharge in the Kangaroo Position has advantages: lower rates of nosocomial infections have been documented, thus allowing parents (and the whole family) to assume a fully active role in the care of their baby at an earlier time, which improves its adjustment to a situation of grief and the risks of attachment, such as with prematurity.**

Evidence Level: **One RCT, expert opinions**

Level of Consensus: unanimous

Rationale:

The Kangaroo Position is initiated with the baby in hospital, and once completed the successful adaptation of the mother/child pair to the position. Once an adequate feeding strategy has been established, the baby may continue thriving in the hospital or may be discharged from the neonatal unit to rooming-in with their mother or to the home. The baby should obviously receive the Kangaroo Position continuously until he/she can regulate his/her temperature.

In KMCM there is less trauma associated with the transition between the hospital and the home given the less abrupt and less intense emotional and physical changes, due to the permanent presence of the parents as caregivers for their child (hospital kangaroo adaptation). The permanent Kangaroo Position enables an appropriate control of the temperature in the hospital and at home (see chapter on Kangaroo Position). There is empirical evidence showing that the early discharge in the Kangaroo Position results not only in no additional problems or re-hospitalization but it also protects against the risks of serious hospital infections [12; 13].

Even though early discharge is not a priority in developed countries for economic reasons, this aspect of KMCM, resulting in a shorter stay with no additional risk for the quality of life in preterm babies, should be considered. One of the main reasons for keeping a "healthy" preterm baby in the neonatal unit is to ensure the baby's thermal regulation. There is sufficient evidence showing that the temperature in the Kangaroo Position is at least as good as that obtained in an incubator, provided it is continually maintained (24 hours a day). Furthermore, the baby in the prolonged Kangaroo Position grows better than the baby in an incubator (see chapter on position). KMCM also prepares the parents to assume responsibilities and to understand the needs of their baby[14]. Once completed a successful kangaroo hospital adaptation, early discharge in the Kangaroo Position should be considered in any institution in any country once the child meets the eligibility criteria in order to move on for an ambulatory kangaroo mother program

The study by Charpak et al[13] showed that the length of hospital stay was lower in the KMCM group particularly for NBs <1500g. Early discharge in the KMCM group did not imply further risks for babies up to 40 weeks' post-conceptional age and up to the first year of corrected age.

2. AMBULATORY KANGAROO FOLLOW-UP

2.1 Follow-up until Term

Question: **Why maintain the kangaroo follow-up until 40 weeks of post-conceptional age?**

Evidence-based Answer: **The preterm infant needs specific monitoring until reaching the gestational age they were expected to be born at in normal circumstances, after appropriate intrauterine development and maturation. Nutrition and the rate of somatic growth should be especially monitored in an attempt to make the baby attain adequate weight and length once he/she reaches the normal term of gestation. The mother and/or caregivers should also be followed up and they should receive emotional support for baby care at home with the KMCM methodology.**

Evidence Level: **expert opinions**

Level of Consensus: unanimous

Rationale:

The care kangaroo of the child already stable but still not regulating their temperature, search to attend it so that it recovers and compensates the deleterious effects to have interrupted its normal gestation, and to take it to term in the possible closest conditions to which had had if it had been born at term and healthy.

The period of "stable growth" is usually defined as the period since the transition is completed around the first 10 days of post-natal life (generally with suboptimal nutrition) until the baby reaches full term. During this period preterm, babies should receive adequate nutrition to attain nutrient accretion and weight gain rates in such a way to normalize both their nutritional status and body composition. Even some catch-up growth is expected and growth during this period should by no means be sub-optimal. For that reason, whether in hospital or an ambulatory environment, a close monitoring is kept and appropriate interventions are carried out through the so-called "kangaroo follow-up".

Above all, the nutritional aim is to achieve adequate nutrition possibly including catch-up growth. With the kangaroo feeding strategies it is possible to make the baby attain weights and lengths during the follow-up similar to those expected for full term babies[15]. Additionally, the baby's performance is monitored, screened for neurological disorders[16], particularly changes in tone which can be early and sensitive predictors of neuromotor alterations, and the retinopathy of prematurity is diagnosed and treated[17]. Ambulatory care also tries to detect and treat other diseases inherent in this period in life for which pharmacological and non-pharmacological measures can be implemented for specific risks: apnea of prematurity with prophylactic methylxanthines, gastroesophageal reflux (Kangaroo Position and prophylactic metoclopramide), and anemia (early ferrous sulfate). The suggested treatments are described in point 3 of PRACTICAL RECOMMENDATIONS of this document.

Evidence for routine use of methylxanthines is equivocal. Given early (transitional period) they can decrease the risk of apnea and the need for ventilation[18] particularly if used therapeutically[19], but apparently its prophylactic use in preterm infants does not result in clear benefits[20]. Methylxanthines are as effective as doxapram[21]; and caffeine (not available in Colombia) is more effective than theophylline[22].

Prophylactic use of metoclopramide to prevent the condition triggered by the gastroesophageal reflux (GOR) is also controversial, though some effectiveness in infants has been recognized[23]. Undoubtedly, the drug has a much better safety profile compared to cisapride, a drug associated with risks of severe arrhythmias in children[24]. Domperidone, a low efficacy neuroleptic with a high potential to generate severe arrhythmias given either parenterally[25] or orally[26], does not make an appropriate alternative for the chemoprophylaxis of GOR.

The decision of maintaining a kangaroo follow-up until 40 weeks is not arbitrary. Reaching full term is an important milestone in the development both of the fetus and of the preterm baby, and the chronological age of the preterm infant must be adjusted according to gestational age at birth, to evaluate growth and development sensibly. The American Academy of Pediatrics (AAP) suggests the use of the corrected age for neurodevelopmental assessments of infants born at less than 40 weeks of gestational age during the first 2 to 3 years of life. The Academy suggests full term gestational age until week 40 (referred to in this document as post-conceptional age) and from full term on, "corrected age" (postnatal age "brought" to term) [27].

2.2 Follow-up after Term

Question: **What are the aims and the follow-up strategy of a kangaroo child after reaching full term?**

Evidence-based Answer: **These guides do not aim at discussing about the healthcare of preterm infants and in general of high-risk newborn infants after reaching full term, which is the primary scope of the care strategies covered by the KMCM. Of note, however, is the fact that these children still need systematic and specific care that includes surveillance of their growth and development, early problem detection, specific therapies, and rehabilitation. This type of systematic activities corresponds to the follow-up programs of high-risk babies, usually extending at least during the first year of life. In many healthcare systems the ambulatory kangaroo programs pioneered the systematic management and follow-up of high-risk newborn infants, to the extent that KMCM is frequently identified with this follow-up.**

Evidence Level: **program assessments, expert consensus and recommendations.**

Level of Consensus: unanimous

Rationale:

Even if the intrinsic value of life of a high-risk preterm babies was not adequately considered, it would be financially unreasonable not to provide care to high-risk infants after the post-neonatal period. Even when the objective is to keep at bay the commonly high healthcare resource investments, it is reasonable to have appropriate follow-up, detection and early intervention programs for these babies discharged from neonatal units. These guides are not addressed at examining the evidence or recommending appropriate strategies for the follow-up of high-risk infants, including of course babies receiving KMCM.

However, it is appropriate to highlight at least some of the attributes such follow-up and management strategies should have:

- Appropriate monitoring of somatic growth and neurological and psychomotor development, with comparisons to adequate standards.
- Screening of sense organs: visual acuity, visual disturbances, auditory acuity. Use of early and appropriate measures of defect correction and rehabilitation.
- Active and occasionally passive immunization.

3. PRACTICAL RECOMMENDATIONS ON KANGAROO POSITION DISCHARGE AND AMBULATORY FOLLOW-UP

3.1 Outline

The kangaroo follow-up with early discharge from the neonatal unit in the Kangaroo Position is one of the basic components of the Kangaroo Mother Care Method and is assimilated to home neonatology until the baby reaches full term or 2500g in the case of a hypotrophic infant, date in which the kangaroo follow-up theoretically ends.

In Colombia a follow-up up to at least one year of corrected age has always been included within the kangaroo follow-up. Kangaroo babies belong to the category of high biological risk of inadequate somatic growth and presenting sensory and neuro-psychomotor development deficits. Although this is not directly addressed by this guide, a high-risk infant follow-up is essential after completing the kangaroo follow-up period per (40-week post-conceptional age or weight 2500 g, whatever happens later), and consequently, the minimal activities to do during this high risk follow-up program are enumerated at the end.

Providing kangaroo care is a continuous process. The Kangaroo Position and feeding are initiated at some time during hospitalization. This marks the beginning of the kangaroo adaptation, which is continued as long as the baby needs it, regardless of whether the infant is in hospital or not. In fact, after a successful adaptation of the mother and the baby to the Kangaroo Position and feeding, evidence shows that the hospital can offer very little which cannot be given to both in an appropriate ambulatory setting.

3.2 Why Seek an Earlier Discharge of Preterm Infants?

The mother-baby separation is a painful though indispensable phase during the first stages for preterm and/or sick LBW infant care. The altered physiology of these immature preterm babies, born too early, needs special care administered by expert health professionals who should be available at any time during day or night. Parents feel like guests, witnesses to a drama that affects them but that they do not understand and in which they feel they cannot step in, irrespective of their role as parents. At a given time, most of these babies adapt to extrauterine life and at this time it is necessary to return them to the care of his parents, first in the hospital and then at home.

When is a baby ready to leave the neonatal unit and be taken home? When is their family ready to receive them? How measure and balance up the risk of a prolonged separation from the parents against the risk of being at home far from electronic and clinical surveillance, and from a possible emergency intervention? How should parents be trained and encouraged to properly handle the new member of the family when they return home?

Most of the institutions have developed rules and protocols for home discharge, based mainly on biological data such as reaching certain weight or post-conceptional age, and many already recognize the need for adequately training parents and giving them support and follow-up for a long time at home. But these rules are not standardized, and they vary depending on the countries and within a single country depending on the institution. They are sometimes arbitrary, unrelated to family or reality.

Intuitively, sending a baby home as soon as possible may appear attractive. But this should not be the objective. It is necessary to specify what is meant by "possible". Neonatologists tend to be conservative when deciding on the appropriate timing. The potential risks and the great investment to save these frail babies result in an overestimation of the risks in relation to the benefits of leaving as soon as possible to the care of the parents.

In the KMCM, the kangaroo follow-up with early discharge from the neonatal unit is a basic component. The benefits of returning parents the rights to be the better caregivers for their frail baby, once a successful kangaroo adaptation is completed.

3.3 Adaptation to the Kangaroo Position

It is a crucial step for the success of the KMCM, for an appropriate discharge in the Kangaroo Position and for the kangaroo follow-up. It may be defined as a process of social, emotional and physical adjustment of the mother and of preterm and/or low birthweight infant's family to the kangaroo methodology. This is achieved through a clear, objective process of education, including training and social and emotional support.

Low birthweight babies are eligible for the KMCM as soon as they have stabilized adequately, are gaining weight in a neutral thermal environment and tolerate the manipulations (whether hospitalized in the intensive o basic or minimal care unit). Each neonatal unit should define its criteria for entry in the kangaroo neonatal adaptation for both mother and for baby. If the family agrees, a member of the kangaroo team (usually a nurse) initiates the adaptation with the mother-child dyad. This is done beside the incubator or in the kangaroo adaptation room of the neonatal unit where available. If the child is ventilated or under CPAP or IV saline, the kangaroo adaptation is initiated beside the incubator. If the baby has a KT and oxygen by nasal cannula, they can be taken to the kangaroo adaptation room. Ideally, this kangaroo collective adaptation room should be part of the neonatal unit and have oxygen connections. The functions of infant adaptation, such as the thermal regulation when in the Kangaroo Position, as well as the ability to coordinate breathing, suction and swallowing should be carefully observed. The mother's ability to hold or carry and breast-feed her baby is also encouraged.

Mothers are encouraged to spend most of the time with her babies. Ideally, mothers who are in the kangaroo adaptation would remain with their babies 24 hours a day but this is not always possible. If this is the case, the kangaroo adaptation is implemented by observing mothers handling their babies for most of the available time each day.

3.4 What Are the Objectives of the Adaptation to the Kangaroo Position while in Hospital?

- To help mothers accept the image of the small baby she has made through permanent contact, the recognition of their characteristics and learning baby care.

- To relieve the maternal stress resulting from looking after a frail preterm baby.
- To attenuate fears and concerns enabling mothers to share them in a group and working out many of them with appropriate information.
- To educate collectively on kangaroo mother care and the characteristics that differentiate a preterm infant from a term infant, the precautions and danger signs of the baby in the Kangaroo Position at home.
- To train mothers in preterm infant feeding: direct breastfeeding, extraction and storage of breast milk and appropriate administration (without baby bottles, using a cup, drip, syringe, etc.) of extracted milk and of other nutrients.
- To reduce the fatigue through physical and relaxation exercise with the baby in the Kangaroo Position.
- To reduce the possible fears about the kangaroo methodology with reports by mothers who have previously participated in the program.
- To foster the physical recognition and a mother-child stimulating relationship through massage to the baby while in skin-to-skin contact.
- To make possible that mothers are capable of looking after of their babies at home, using the kangaroo methodology, training on how to hold the baby 24 hours a day.
- To reduce the fears and concerns while the KMCM is provided.
- To promote and strengthen the development of the mother-child emotional bonding.
- To evaluate whether babies are ready and capable of receiving ambulatory KMCM.

3.5 What Does a Successful Adaption to the Kangaroo Position while in Hospital Imply?

- The baby gains weight daily in the neonatal unit.
- The baby has his/her mother or a relative who knows how to feed and carry them in the Kangaroo Position.
- A baby's mother or relative, who feel capable of following the steps and procedures of the home kangaroo intervention and who showed their interest in participating in the hospital kangaroo adaptation.
- Both mother and relatives are committed with the ambulatory kangaroo follow-up.

3.6 What are the Criteria for Hospital Discharge in the Kangaroo Position?

A baby is ELIGIBLE for discharge, regardless of their weight or gestational age if:

- regulates their temperature in the Kangaroo Position.
- has an adequate weight gain in the neonatal unit in the Kangaroo Position and incubator.
- has completed their treatment, if any.
- If they receive oxygen through a nasal cannula, it should be lower than 1/2 l/mn.
- has gone through a successful hospital kangaroo adaptation:
  - Appropriate breastfeeding techniques (direct suction from the breast) and milk expression,
  - Mother's acceptance and education in the kangaroo methodology,
  - Family and social support,
  - Adequate suck-swallow-breathe coordination
- There is a kangaroo mother program ready to provide a kangaroo follow-up.

The mother is eligible if:

- She feels able to care for her baby with the kangaroo methodology (position and nutrition) at home.
- There is family commitment (mother, father and grandmothers) to be involved in the kangaroo follow-up.
- There are no physical contraindications for the Kangaroo Position (see chapter on Position).
- For high-risk social cases a multidisciplinary team concept is required for the discharge: prostitute mother, single mother with twins, single mother with a child requiring ambulatory oxygen...etc.

3.7. What is the Kangaroo Follow-up Like?

This follow-up implies a physical structure known as Kangaroo Mother Program, involving a multi-disciplinary team trained in KMCM. Young children in the Kangaroo Position and older children presenting either for their neurological or psychomotor development screening tests or their growth control are found in consultations. Consultations admit healthy not sick children to avoid contamination from one another. These collective meetings are relevant for anxiety management as these parents always are concerned about the future of their frail and different babies.

It should be located within a hospital structure, ideally in a location with professionals who know how to handle sick infants.

- Because it is home neonatal care.
- Because kangaroo emergencies involve neonates and must be treated in a neonatal unit or at least by adequately trained individuals.
- Because follow-up is at first daily with weight-taking on electronic scales and examination by a pediatrician capable of detecting any change in this frail baby who cannot speak.
- Because the ambulatory kangaroo adaptation may take the whole morning or all day or several days if there is no weight gain or should lactation problems arise

Facilities: There should be a large collective consultation and waiting room. Furthermore, it should involve two separated locations where the ambulatory kangaroo adaptation may take place in one and another for psychology consultations, workshops for new parents and psychomotor development examinations.

A multidisciplinary team is available: pediatrician, nurse, psychologist, social worker, nutritionist, physical therapist, ophthalmologist, optometrist, speech therapist, each contributing from their discipline

It is a collective consultation

- because education takes place daily and is collective, which makes it possible to reinforce knowledge as the mother listens to the same talks several times.
- because mothers waiting for their turns listen to other people's problems and share their experiences and difficulties with other mothers.
- because anxiety is better dealt with: by watching smaller babies than theirs, mothers confirm that their babies are in better shape; watching the larger ones provides them with an objective to attain.
- because a psychologist is available in case of depression, loneliness, and insecurity.
- because the commitment of daily consultations somehow mirrors the same commitment when babies are hospitalized and daily visits to the hospital are necessary to be with them. It is necessary to remind parents that it is about hard work for a short time, until the baby reaches 40 weeks, and that this results in lifelong benefits.
- It stimulates solidarity in the family, particularly when the child is oxygen dependent, since to be able to mobilize after the consultation an accompanying person to help with the oxygen canister is needed apart from the mother.

Ambulatory Kangaroo Adaptation

It may last from a day for well trained mothers to a week for mothers with difficulties in feeding their baby or when there is inadequate growth. The adaptation is supervised by a nurse trained in maternal feeding techniques and may be supported by psychologists and social workers.

- It is initiated on the first day of entry in the kangaroo mother program.
- Professionals with dedication, patience, persistence, and human warmth, capable of making mothers trust their own capacities, who are available to solve any concern, or repeat explanations, are required.
- The risk of hypoglycemia needs to be considered.
- A close supervision of the way mothers look after their babies at home with the kangaroo methodology is required.
- Supervision as to the use and management of nutrient supplementation in babies hospitalized for prolonged periods while achieving occasional exclusive breastfeeding is required.
- Whatever was learned in the hospital adaptation should be reinforced.
- "Sunbath" taking for physiological jaundice should be taught.
- Massage technique in the Kangaroo Position should be reinforced.
- Offering continuous emotional support for the mother and the family is required.

The kangaroo follow-up to at least 1 year of corrected age:

- At first follow-up is daily: nutrition and quality of the food the child receives is evaluated and a weight gain

of around 15g/kg/d until it reaches 37 weeks (speed of intrauterine growth) is expected. Then, growth is expected to be 8-11g/kg/d up to the age of 40 weeks of post-conceptional age. Length should increase an average of 0.8 cm. per week, and head circumference between 0.5 and 0.8 cm. until full term.

The follow-up becomes weekly when the child fulfills with the adequate growth, which it shows that there already exist a harmony and equilibrium among the parents and the child. If parents live too far, help is provided to parents to encourage the consultation despite the difficulties, in the same way as they are encouraged to visit their baby daily when hospitalized.

If daily consultation by one of the parents is not possible, because of absolute poverty, or lack of transport, or because they live too much far, early discharge can be given to rooming-in (for example in a hospital wing) until complete discharge is possible, making sure that parents return for a weekly follow-up.

- The way parents managed with the kangaroo methodology is checked. Usually the first nights are very difficult and parents should be encouraged that they are learning to rest with their baby in the Kangaroo Position, and are satisfied when babies show adequate growth. They feel proud to know that this is the result of their effort.

- All babies go through a first session of kangaroo adaptation on the first ambulatory day and, upon the mother's request or when somatic growth is inadequate, the following days. The decision to supplement breastfeeding with preterm formula and the moment to initiate it should be a multidisciplinary decision. The technique was described in the chapter on kangaroo nutrition. In case of initiation, it should be confirmed that the mother knows the hygiene rules necessary for the use of this type of food as well as the administration techniques using a drip, cup, or syringe to try to interfere as little as possible in breastfeeding. The objective is always to achieve full term with exclusive breastfeeding.

- Medication
  Anti-reflux drugs are given until full term and then according to symptoms.
  Caffeine or Xanthines: PTNB with gestational age 34 weeks at KMP entry and continued until full term.
  Vitamin A, D, E, K until full term.
  Ferrous sulfate since the 30 days and up to one year of corrected age.

- Screenings:
  -. Ophthalmologic: starting at 34 weeks or at 28 days of birth,
  -. Neurological: Tone evaluation until full term and then complete neurological assessment during the first year of corrected follow-up. The neurological screening can be performed when the child reaches the 40 weeks, then at 3, 6, 9 and 12 months. This enables an appropriate referral to physical therapy, in the case of babies with developmental disorders, assessing the impact on the following neurological examinations. The parents are encouraged to learn the therapy exercises to do them at home and thus reinforce the treatment.
  -. Psychomotor development: minimum twice a year. The applied test should take into account all the aspects of development: not only psychomotor but also social factors. It can be complemented with a series of exercises to at home, which parents are taught during the assessment session.
  -. Brain ultrasound scan. It is important to have a first cerebral image of this high-risk baby before full term. In babies with normal tone and neuro-psychomotor development no complementary examination is repeated. In babies with normal and/or abnormal brain ultrasound scans and abnormal neuro-psychomotor development during the first year, a brain CT and/or MRI should be used if required.
  -. Using hip x-rays: in all the children up to 3 months of corrected age.
  -. Audiometry: starting at 3 months of corrected age.
  -. Optometry: starting at 3 months of corrected age.

- Somatic growth during follow-up up to one year of corrected age:
  Controls are distributed throughout the year trying to match screenings and immunization schedules in order to save trips to the parents.
  Point zero in growth curves corresponds to 40 weeks of age, ideally somatic growth curves where growth before and after full term is represented in the same graphic for weight, length and head circumference should be used.

- Educational sessions: they are carried out daily in collective consultation on subjects concerning both smaller and larger infants. The mother to a baby in Kangaroo Position attending consultations on a daily basis should have listened to the talk on complementary feeding several times before her baby gets to the age in which complementary feeding is initiated. Psychologist and nurse, nutritionist and pediatrician share educational sessions, which are repeated and short.

- Vaccines: They can be given in the kangaroo mother program. It is necessary to meet requirements by healthcare authorities as regards physical and personal structure. They can also be given in the hospital or any other location meeting these requirements. Immunization within a kangaroo mother program may guarantee greater compliance and smaller losses to follow-up. Each country has its own immunization schedule; however, due to the neurological fragility, it is desirable to give the inactivated polio and the acellular pertussis vaccines to these high-risk babies participating in the kangaroo collective consultations.

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APPENDIX 1: "Spain Agree"

APPENDIX 2

Medline

1.	Meta-Analysis/
2.	meta analy$.tw.
3.	metaanaly$.tw.
4.	meta analysis.pt.
5.	(systematic adj (review$1 or overview$1)).tw.
6.	exp Review Literature/
7.	or/1-6
8.	cochrane.ab.
9.	embase.ab.
10.	(psychlit or psyclit).ab.
11.	(psychinfo or psycinfo).ab.
12.	(cinahl or cinhal).ab.
13.	science citation index.ab.
14.	bids.ab.
15.	cancerlit.ab.
16.	or/8-15
17.	reference list$.ab.
18.	bibliograph$.ab.
19.	hand-search$.ab.
20.	relevant journals.ab.
21.	manual search$.ab.
22.	or/17-21
23.	selection criteria.ab.
24.	data extraction.ab.
25.	23 or 24
26.	review.pt.
27.	25 and 26
28.	comment.pt.
29.	letter.pt.
30.	editorial.pt.
31.	animal/
32.	human/
33.	31 not (31 and 32)
34.	or/28-30,33
35.	7 or 16 or 22 or 27
36.	35 not 34

Embase

1.	exp Meta Analysis/
2.	((meta adj analy$) or metaanalys$).tw.
3.	(systematic adj (review$1 or overview$1)).tw.
4.	or/1-3
5.	cancerlit.ab.
6.	cochrane.ab.
7.	embase.ab.
8.	(psychlit or psyclit).ab.
9.	(psychinfo or psycinfo).ab.
10.	(cinahl or cinhal).ab.
11.	science citation index.ab.
12.	bids.ab.
13.	or/5-12
14.	reference lists.ab.
15.	bibliograph$.ab.
16.	hand-search$.ab.
17.	manual search$.ab.
18.	relevant journals.ab.
19.	or/14-18
20.	data extraction.ab.
21.	selection criteria.ab.
22.	20 or 21
23.	review.pt.
24.	22 and 23
25.	letter.pt.
26.	editorial.pt.
27.	animal/
28.	human/
29.	27 not (27 and 28)
30.	or/25-26,29
31.	4 or 13 or 19 or 24
32.	31 not 30

CINAHL

1	Meta analysis/
2	Meta analys$.tw.
3	Metaanaly$.tw.
4	exp Literature review/
5	(systematic adj (review or overview)).tw.
6	Or/1-5
7	Commentary.pt.
8	Letter.pt.
9	Editorial.pt.
10	Animals/
11	Or/7-10
12	6 not 11

Randomised Controlled Trials
The search filter used by SIGN to retrieve randomised controlled trials has been adapted from the first two sections of strategy designed by the Cochrane Collaboration identifying RCTs for systematic review.

Medline

1	Randomized controlled trials/
2	Randomized controlled trial.pt.
3	Random allocation/
4	Double blind method/
5	Single blind method/
6	Clinical trial.pt.
7	Exp clinical trials/
8	Or/1-7
9	(clinic$ adj trial$1).tw.
10	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
11	Placebos/
12	Placebo$.tw.
13	Randomly allocated.tw.
14	(allocated adj2 random).tw.
15	Or/9-14
16	8 or 15
17	Case report.tw.
18	Letter.pt.
19	Historical article.pt.
20	Review of reported cases.pt.
21	Review, multicase.pt.
22	Or/17-21
23	16 not 22

Embase

1	Clinical trial/
2	Randomized controlled trial/
3	Randomization/
4	Single blind procedure/
5	Double blind procedure/
6	Crossover procedure/
7	Placebo/
8	Randomi?ed controlled trial$.tw.
9	Rct.tw.
10	Random allocation.tw.
11	Randomly allocated.tw.
12	Allocated randomly.tw.
13	(allocated adj2 random).tw.
14	Single blind$.tw.
15	Double blind$.tw.
16	((treble or triple) adj (blind$).tw.
17	Placebo$.tw.
18	Prospective study/
19	Or/1-18
20	Case study/
21	Case report.tw.
22	Abstract report/ or letter/
23	Or/20-22
24	19 not 23

CINAHL

1	Exp clinical trials/
2	Clinical trial.pt.
3	(clinic$ adj trial$1).tw.
4	((singl$ or doubl$ or trebl$ or tripl$) adj blind$3 or mask$3)).tw.
5	Randomi?ed control$ trial$.tw.
6	Random assignment/
7	Random$ allocat$.tw.
8	Placebo$.tw.
9	Placebos/
10	Quantitative studies/
11	Allocat$ random$.tw.
12	Or/1-11

Observational Studies

The Observational Studies search filter used by SIGN has been developed in-house to retrieve studies most likely to meet SIGN's methodological critieria.

Medline

1	Epidemiologic studies/
2	Exp case control studies/
3	Exp cohort studies/
4	Case control.tw.
5	(cohort adj (study or studies)).tw.
6	Cohort analy$.tw.
7	(Follow up adj (study or studies)).tw.
8	(observational adj (study or studies)).tw.
9	Longitudinal.tw.
10	Retrospective.tw.
11	Cross sectional.tw.
12	Cross-sectional studies/
13	Or/1-12

Embase

1	Clinical study/
2	Case control study
3	Family study/
4	Longitudinal study/
5	Retrospective study/
6	Prospective study/
7	Randomized controlled trials/
8	6 not 7
9	Cohort analysis/
10	(Cohort adj (study or studies)).mp.
11	(Case control adj (study or studies)).tw.
12	(follow up adj (study or studies)).tw.
13	(observational adj (study or studies)).tw.
14	(epidemiologic$ adj (study or studies)).tw.
15	(cross sectional adj (study or studies)).tw.
16	Or/1-5,8-15

CINAHL

1 Prospective studies/
2 Exp case control studies/
3 Correlational studies/
4 Nonconcurrent prospective studies/
5 Cross sectional studies/
6 (cohort adj (study or studies)).tw.
7 (observational adj (study or studies)).tw.

Diagnostic Studies

The Diagnostic Studies search filter used by SIGN has been adapted from the filter designed by the Health Information Research Unit of the McMaster University, Ontario.

Medline

1 exp "Sensitivity and Specificity"/
2 sensitivity.tw.
3 specificity.tw.
4 exp DIAGNOSIS/
5 exp PATHOLOGY/
6 ((pre test or pretest) adj probability).tw.
7 post test probability.tw.
8 predictive value$.tw.
9 likelihood ratio$.tw.
10 false negative$.tw.
11 false positive$.tw.
12 screening.tw.
13 (diagnosis or diagnostic).tw.
14 (diagnosis or diagnostic).af.
15 exp Mass Screening/
16 or/1-15

Embase

1 exp EPIDEMIOLOGY/
2 sensitivity.tw.
3 specificity.tw.
4 exp DIAGNOSIS/
5 (diagnosis or diagnostic).af.
6 (diagnosis or diagnostic).tw.
7 ((pre test or pretest) adj probability).tw.
8 post test probability.tw.
9 predictive value$.tw.
10 likelihood ratio$.tw.
11 false negative$.tw.
12 false positive$.tw.
13 screening.tw.
14 exp SCREENING/
15 or/1-14

CINHAL

1 exp "Sensitivity and Specificity"/
2 sensitivity.tw.
3 specificity.tw.
4 exp DIAGNOSIS/
5 exp PATHOLOGY/
6 ((pre test or pretest) adj probability).tw.
7 post test probability.tw.
8 predictive value$.tw.
9 likelihood ratio$.tw.
10 false negative$.tw.
11 false positive$.tw.
12 screening.tw.
13 (diagnosis or diagnostic).tw.
14 (diagnosis or diagnostic).af.
15 or/1-14

Economic Studies

The economic studies filter used by SIGN is an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination at the University of York.

Medline

1 Economics/
2 "costs and cost analysis"/
3 Cost allocation/
4 Cost-benefit analysis/
5 Cost control/
6 Cost savings/
7 Cost of illness/
8 Cost sharing/
9 "deductibles and coinsurance"/
10 Medical savings accounts/
11 Health care costs/
12 Direct service costs/
13 Drug costs/
14 Employer health costs/
15 Hospital costs/
16 Health expenditures/
17 Capital expenditures/
18 Value of life/
19 Exp economics, hospital/
20 Exp economics, medical/
21 Economics, nursing/
22 Economics, pharmaceutical/
23 Exp "fees and charges"/
24 Exp budgets/
25 (low adj cost).mp.
26 (high adj cost).mp.
27 (health?care adj cost$).mp.
28 (fiscal or funding or financial or finance).tw.
29 (cost adj estimate$).mp.
30 (cost adj variable).mp.

31	(unit adj cost$).mp.
32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
33	Or/1-32

Embase

1	~~Socioeconomics/~~
2	Cost benefit analysis/
3	Cost effectiveness analysis/
4	Cost of illness/
5	Cost control/
6	Economic aspect/
7	Financial management/
8	Health care cost/
9	Health care financing/
10	Health economics/
11	Hospital cost/
12	(fiscal or financial or finance or funding).tw.
13	Cost minimization analysis/
14	(cost adj estimate$).mp.
15	(cost adj variable$).mp.
16	(unit adj cost$).mp.
17	Or/1-16

CINAHL

1	~~Exp economics/~~
2	Exp “financial management”/
3	Exp “financial support”/
4	Exp “financing organized”/
5	Exp “business”/
6	Or/2-5
7	1 not 6
8	Health resource allocation.sh.
9	Health resource utilization.sh.
10	8 or 9
11	7 or 10
12	(cost or costs or economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
13	11 or 12
14	Editorial.pt.
15	Letter.pt.
16	News.pt.
17	Or/14-16
18	13 not 17
19	“Animal studies”/
20	18 not 19
21	Cochrane library.so.
22	Anonymous.au.
23	20 not (21 or 22)

APPENDIX 3: Forms of critical apraisal

SIGN	**Methodology Checklist 1: Systematic Reviews and Meta-analyses**	
Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:		Key Question No:
Checklist completed by:		
SECTION 1: INTERNAL VALIDITY		
In a well conducted systematic review		***In this study this criterion is::***
1.1	The study addresses an appropriate and clearly focused question.	Well covered / Adequately addressed / Poorly addressed / Not addressed / Not reported / Not applicable
1.2	A description of the methodology used is included.	Well covered / Adequately addressed / Poorly addressed / Not addressed / Not reported / Not applicable
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered / Adequately addressed / Poorly addressed / Not addressed / Not reported / Not applicable
1.4	Study quality is assessed and taken into account.	Well covered / Adequately addressed / Poorly addressed / Not addressed / Not reported / Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered / Adequately addressed / Poorly addressed / Not addressed / Not reported / Not applicable
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code ++, +, or –*	
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	

SECTION 3: DESCRIPTION OF THE STUDY *Please print answers clearly*				
3.1	What types of study are included in the review? *(Highlight all that apply)*	RCT Case-control	CCT Other	Cohort
3.2	How does this review help to answer your key question? *Summarise the main conclusions of the review and how it relates to the relevant key question. Comment on any particular strengths or weaknesses of the review as a source of evidence for a guideline produced for the NHS in Scotland.*			

SIGN

Methodology Checklist 2: Randomised Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study…..	***In this study this criterion is::***	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias? *Code ++, +, or –*	
2.2	If coded as +, or – what is the likely direction in which	

	bias might affect the study results?	
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	
SECTION 3: DESCRIPTION OF THE STUDY (The following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). *PLEASE PRINT CLEARLY*		
3.1	How many patients are included in this study? *Please indicate number in each arm of the study, at the time the study began.*	
3.2	What are the main characteristics of the patient population? *Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based*	
3.3	What intervention (treatment, procedure) is being investigated in this study? *List all interventions covered by the study.*	
3.4	What comparisons are made in the study? *Are comparisons made between treatments, or between treatment and placebo / no treatment?*	
3.5	How long are patients followed-up in the study? *Length of time patients are followed from beginning participation in the study. Note specified end points used to decide end of follow-up (e.g. death, complete cure). Note if follow-up period is shorter than originally planned.*	
3.6	What outcome measure(s) are used in the study? *List all outcomes that are used to assess effectiveness of the interventions used.*	
3.7	What size of effect is identified in the study? *List all measures of effect in the units used in the study – e.g. absolute or relative risk, NNT, etc. Include p values and any confidence intervals that are provided.*	
3.8	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.9	Does this study help to answer your key question? *Summarise the main conclusions of the study and indicate how it relates to the key question.*	

SIGN

Methodology Checklist 3: Cohort studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted cohort study:	***In this study the criterion is:***	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
SELECTION OF SUBJECTS			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	*Comparison is made between full participants and those lost to follow up, by exposure status.*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
ASSESSMENT			
1.7	The outcomes are clearly defined.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	The assessment of outcome is made blind to exposure status.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	The measure of assessment of exposure is reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.12	Exposure level or prognostic factor is assessed more than once.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?		
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code ++, +, or –*		
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?		
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?		
SECTION 3: DESCRIPTION OF THE STUDY (*Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).*			
	PLEASE PRINT CLEARLY		
3.1	*How many patients are included in this study?* ***List the number in each group separately***		
3.2	What are the main characteristics of the study population? *Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based*		
3.3	What environmental or prognostic factor is being investigated in this study?		
3.4	What comparisons are made in the study? ***Are comparisons made between presence or absence of an environmental / prognostic factor, or different levels of the factor??***		
3.5	For how long are patients followed-up in the study?.		
3.6	What outcome measure(s) are used in the study? *List all outcomes that are used to assess the impact of the chosen environmental or prognostic factor.*		

3.7	What size of effect is identified in the study? *List all measures of effect in the units used in the study – e.g. absolute or relative risk. Include p values and any confidence intervals that are provided.* ***Note****: Be sure to include any adjustments made for confounding factors, differences in prevalence, etc.*	
3.8	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.9	Does this study help to answer your key question? Summarise the main conclusions of the study and indicate how it relates to the key question.?	

Methodology Checklist 4: Case-control studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In an well conducted case control study:	***In this study the criterion is:***	
1.1	The study addresses an appropriate and clearly focused question	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
	SELECTION OF SUBJECTS		
1.2	The cases and controls are taken from comparable populations	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The same exclusion criteria are used for both cases and controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	What percentage of each group (cases and controls) participated in the study?	Cases: Controls:	
1.5	Comparison is made between participants and non-participants to establish their similarities or differences	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	Cases are clearly defined and differentiated from controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	*It is clearly established that controls are non-cases*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
	ASSESSMENT		
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.9	Exposure status is measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
	CONFOUNDING		
1.10	The main potential confounders are identified and taken into account in the design and analysis	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
	STATISTICAL ANALYSIS		
1.11	Confidence intervals are provided		

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	*How well was the study done to minimise the risk of bias or confounding?* *Code ++, +, or –*	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
SECTION 3: DESCRIPTION OF THE STUDY (*Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).*		
	PLEASE PRINT CLEARLY	
3.1	*How many patients are included in this study?* ***List the number cases and controls separately***	
3.2	What are the main characteristics of the study population? *Include all characteristics used to identify both cases and controls – e.g. age, sex, social class, disease status*	
3.3	What environmental or prognostic factor is being investigated in this study?	
3.4	**What comparisons are made in the study?** Normally only one factor will be compared, but in some cases the extent of exposure may be stratified – e.g. non-smokers v. light, moderate, or heavy smokers. Note all comparisons here.	
3.5	For how long are patients followed-up in the study? *Length of time participant histories are tracked in the study.*	
3.6	What outcome measures are used in the study? *List all outcomes that are used to assess the impact of the chosen environmental or prognostic factor.*	
3.7	What size of effect is identified in the study? *Effect size should be expressed as an odds ratio. If any other measures are included, note them as well. Include p values and any confidence intervals that are provided.*	
3.8	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.9	Does this study help to answer your key question? Summarise the main conclusions of the study and indicate how it relates to the key question.?	

SIGN

Methodology Checklist 5: Studies of Diagnostic Accuracy

Study identification (*Include author, title, reference, year of publication*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted diagnostic study…	***In this study this criterion is***	
1.1	The nature of the test being studied is clearly specified.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The test is compared with an appropriate gold standard.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	*Where no gold standard exists, a validated reference standard is used as comparator.*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	*Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population.*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	*The test and gold standard are measured independently (blind) of each other.*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The test and gold standard are applied as close together in time as possible.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	Results are reported for all patients that are entered into the study.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	*A pre-test diagnosis is made and reported.*	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How reliable are the conclusions of this study? Code ++, +, or –	
2.2	Is the spectrum of patients assessed in this study comparable with the patient group targeted by this guideline in terms of the proportion with the disease, or the proportion with severe versus mild disease?	

SECTION 3: DESCRIPTION OF THE STUDY (*Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).* **PLEASE PRINT CLEARLY**		
3.1	How many patients are included in this study? *Please indicate number of patients included, with inclusion/exclusion criteria used to select them.*	
3.2	What is the prevalence (proportion of people with the disease being tested for) in the population from which patients were selected?	
3.3	What are the main characteristics of the patient population? *Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based*	
3.4	What test is being evaluated in this study? *Consider whether the technology being described is comparable / relevant to the test being considered in the guideline. i.e. make sure the test has not been superseded by later developments.*	
3.5	What is the reference standard with which the test being evaluated is compared? *Indicate whether a gold standard, or if not how this standard was validated.*	
3.7	*What is the estimated sensitivity of the test being evaluated? (state 95% CI)* *Sensitivity = proportion of results in patients with the disease that are correctly identified by the new test.*	
3.8	*What is the estimated specificity of the test being evaluated? (state 95% CI)* *Specificity = proportion of results in patients without the disease that are correctly identified by the new test*	
3.9	*What is the positive predictive value of the test being evaluated?* *Positive predictive value = proportion of patients with a positive test result that actually had the disease.*	
3.10	What is the negative predictive value of the test being evaluated? *Negative predictive value = proportion of patients with a negative test result that actually did not have the disease.*	
3.11	What are the likelihood ratios for the test being evaluated? *If not quoted in the study, a number of tools are available that simplify calculation of LRs. Please indicate where results are calculated rather than taken from the study.*	
3.12	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.13	Are there any specific issues raised by this study? *How does this study help to answer your question?*	

SIGN

Methodology Checklist 6: Economic Evaluations

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted economic study.....	***In this study this criterion is::***	
1.1	There is a defined and answerable study question	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The economic importance of the question is clear	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	The choice of study design is justified	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	If discounting of future costs and outcomes is necessary, it been performed correctly	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	Assumptions are made explicit and a sensitivity analysis performed	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.9	The results provide information of relevance to policy makers	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	Is this study an economic evaluation, or a cost analysis?	
2.2	How well was the study conducted? *Code ++, +, or –*	

2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	
SECTION 3: DESCRIPTION OF THE STUDY (The following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). **PLEASE PRINT CLEARLY**		
3.1	What interventions are evaluated in this study?	
3.2	What type of study is it (cost-benefit analysis, cost utility study, etc.)?	
3.3	How many patients participated in the study?	
3.4	What was the scale of the incremental cost/benefit?	
3.5	Is any statistical measure of uncertainty given? *e.g. confidence intervals; p values*	
3.4	What are the characteristics of the study population? *e.g. age, sex, disease characteristics of the population, disease prevalence.*	
3.5	What are the characteristics of the study setting? *e.g. rural, urban, hospital inpatient or outpatient, general practice, community.*	
3.6	How many groups/sites are there in the study? *If the study is carried out on more than one group of patients, or at more than one site, indicate how many are involved.*	
3.7	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.8	Does this study help to answer your key question? *Summarise the main conclusions of the study and indicate how it relates to the key question.*	

SIGN 50: A guideline developers' handbook
Notes on the use of Methodology Checklist 1: Systematic Reviews and Meta-analyses

Section 1 identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of study design and to make a judgement as to how well the current study meets each criterion. Each relates to an aspect of methodology that research has shown to be likely to influence the conclusions of a study.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

1.1 The study addresses an appropriate and clearly focused question.

Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions.

1.2 A description of the methodology used is included.

One of the key distinctions between a systematic review and a general review is the systematic methodology used. A systematic review should include a detailed description of the methods used to identify and evaluate individual studies. If this description is not present, it is not possible to make a thorough evaluation of the quality of the review, and **it should be rejected as a source of Level 1 evidence**. (Though it may be useable as Level 4 evidence, if no better evidence can be found.)

1.3 The literature search is sufficiently rigorous to identify all the relevant studies.

A systematic review based on a limited literature search – e.g. one limited to Medline only – is likely to be heavily biased. A well conducted review should as a minimum look at Embase and Medline, and from the late 1990s onward, the Cochrane Library. Any indication that hand searching of key journals, or follow up of reference lists of included studies were carried out in addition to electronic database searches can be taken as evidence of a well conducted review.

1.4 Study quality is assessed and taken into account.

A well conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. If there is no indication of such an assessment, the individual papers included in the review must be obtained and their methodology evaluated.

1.5 There are enough similarities between the studies selected to make combining them reasonable.

Studies covered by a systematic review should be selected using clear inclusion criteria. These criteria should include, either implicitly or explicitly, the question of whether the selected studies can legitimately be compared. It should be clearly ascertained, for example, that the populations covered by the studies are comparable; that the methods used in the investigations are the same; that the outcome measures are comparable; and the variability in effect sizes between studies is not greater than would be expected by chance alone.

Section 2 relates to the overall assessment of the paper. Question 2.1 asks you to rate the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

- ++ **All or most** of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
- \+ **Some** of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
- \- **Few or no** criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.

Question 2.2 asks you to indicate whether a review with poor or relatively poor methodology is likely to overstate or understate any effect identified.

Section 3 asks you to identify the types of study covered by the review, and to provide a brief summary of the conclusions of the review as well as your own view of its strengths and weaknesses, and how it will help to answer the key question.

SIGN 50: A guideline developers' handbook Notes on the use of Methodology Checklist 2: Randomised Controlled Trials

Section 1 identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of RCT design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- o Well covered
- o Adequately addressed
- o Poorly addressed
- o Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- o Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- o Not applicable.

1.1 *The study addresses an appropriate and clearly focused question*

Unless a clear and well defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

1.2 *The assignment of subjects to treatment groups randomised*

Random allocation of patients to receive one or other of the treatments under investigation, or to receive either treatment or placebo, is fundamental to this type of study. **If there is no indication of randomisation, the study should be rejected.** If the description of randomisation is poor, the study should be given a lower quality rating. Processes such as alternate allocation, allocation by date of birth, or day of the week attending a clinic are not true randomisation processes and it is easy for a researcher to work out which patients received which treatment. These studies should therefore be classed as Controlled Clinical Trials rather than RCTs.

1.3 *An adequate concealment method is used*

Allocation concealment refers to the process used to ensure that researchers are unaware which group patients are being allocated to at the time they enter the study. Research has shown that where allocation concealment is inadequate, investigators can overestimate the effect of interventions by up to 40%. Centralised allocation, computerised allocation systems, or the use of coded identical containers would all be regarded as adequate methods of concealment, and may be taken as indicators of a well conducted study. If the method of concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating, and can be rejected if the concealment method is seen as inadequate.

1.4 *Subjects and investigators are kept 'blind' to treatment allocation*

Blinding refers to the process whereby people are kept unaware of which treatment an individual patient has been receiving when they are assessing the outcome for that patient. It can be carried out up to three levels. Single blinding is where patients are unaware of which treatment they are receiving. In double blind studies neither the doctor nor the patient knows which treatment is being given. In very rare cases studies may be triple blinded, where neither patients, doctors, nor those conducting the analysis are aware of which patients received which treatment. The higher the level of blinding, the lower the risk of bias in the study.

1.5 *The treatment and control groups were similar at the start of the trial*

Patients selected for inclusion in a trial must be as similar as possible. The study should report any significant differences in the composition of the study groups in relation to gender mix, age, stage of disease (if appropriate), social background, ethnic origin, or comorbid conditions. These factors may be covered by inclusion and exclusion criteria, rather than being reported directly. Failure to address this question, or the use of inappropriate groups, should lead to the study being downgraded.

1.6 *The only difference between the groups is the treatment under investigation*

If some patients received additional treatment, even if of a minor nature or consisting of advice and counselling rather than a physical intervention, this treatment is a potential confounding factor that may invalidate the results. **If groups were not treated equally, the study should be rejected unless no other evidence is available**. If the study is used as evidence it should be treated with caution.

1.7 *All relevant outcomes measured in a standard, valid and reliable way*

The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected**. Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

1.8 *What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?*

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but this may vary. Some regard should be paid to why patients dropped out, as well as how many. It should be noted that the drop out rate may be expected to be higher in

studies conducted over a long period of time. A higher drop out rate will normally lead to downgrading, rather than rejection of a study.

1.9 *All the subjects are analysed in the groups to which they were randomly allocate (intention to treat analysis)*

In practice, it is rarely the case that all patients allocated to the intervention group receive the intervention throughout the trial, or that all those in the comparison group do not. Patients may refuse treatment, or contra-indications arise that lead them to be switched to the other group. If the comparability of groups through randomisation is to be maintained, however, patient outcomes must be analysed according to the group to which they were originally allocated irrespective of the treatment they actually received. (This is known as intention to treat analysis.) If it is clear that analysis was not on an intention to treat basis, the study may be rejected. If there is little other evidence available, the study may be included but should be evaluated as if it were a non-randomised cohort study.

1.10 *Where the study is carried out at more than one site, results are comparable for all sites*

In multi-site studies, confidence in the results should be increased if it can be shown that similar results were obtained at the different participating centres.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

\+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

\- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.
The aim of the other questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Section 3 asks you to summarise key points about the study that will be added to an evidence table at the next stage of the process. **It is important that you complete this section as fully as possible, and include actual data from the study wherever relevant.**

SIGN 50: A guideline developers' handbook
Notes on the use of Methodology Checklist 3: Cohort studies

The studies covered by this checklist are designed to answer questions of the type "What are the effects of this exposure?", It relates to studies that compare a group of people with a particular exposure with another group who either have not had the exposure, or have a different level of exposure. Cohort studies may be prospective (where the exposure is defined and subjects selected before outcomes occur), or retrospective (where exposure is assessed after the outcome is known, usually by the examination of medical records). Retrospective studies are generally regarded as a weaker design, and should not receive a "++" rating.

Section 1 identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown to be likely to influence the conclusions of a study.

Because of the potential complexity and subtleties of the design of this type of study, there are comparatively few criteria that automatically rule out use of a study as evidence. It is more a matter of increasing confidence in the strength of association between exposure and outcome by identifying how many aspects of good study design are present, and how well they have been tackled. A study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

1.1 *The study addresses an appropriate and clearly focused question?*

Unless a clear and well defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

1.2 *The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.*

It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question. **If the study does not include clear definitions of the source populations and eligibility criteria for participants it should be rejected**.

1.3 *The study indicates how many of the people asked to take part did so, in each of the groups being studied.*

The participation rate is defined as the number of study participants divided by the number of eligible subjects, and should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of selection bias may be present, and the study results should be treated with considerable caution.

1.4 *The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis?*

If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial the final result will be biased. A well conducted study will attempt to estimate the likelihood of this occurring, and take it into account in the analysis through the use of sensitivity studies or other methods.

1.5 *What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?*

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop out rate is a matter of judgement based on the reasons why people dropped out, and whether drop out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.

1.6 *Comparison is made between full participants and those lost to follow-up, by exposure status.*

For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. Any indication that differences exist, should lead to the study results being treated with caution.

1.7 *The outcomes are clearly defined.*

Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart disease in middle aged men, for example, participants might be followed up until death, or until reaching a predefined age. **If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.**

1.8 *The assessment of outcome is made blind to exposure status*

If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.

1.9 *Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.*

Blinding is not possible in many cohort studies. In order to asses the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups - e.g. frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

1.10 The measure of assessment of exposure is reliable.

A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.

1.11 *Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.*

The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

1.12 *Exposure level or prognostic factor is assessed more than once.*

Confidence in data quality should be increased if exposure level is measured more than once in the course of the study. Independent assessment by more than one investigator is preferable.

1.13 *The main potential confounders are identified and taken into account adequately in the design and analysis.*

Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate

which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. **A study that does not address the possibility of confounding should be rejected.**

1.14 *Confidence intervals are provided.*

Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

++ **All or most** of the criteria have been fulfilled.
Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
\+ **Some** of the criteria have been fulfilled.
Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
\- **Few or no** criteria fulfilled
The conclusions of the study are thought likely or very likely to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.

The aim of the other questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Section 3 asks you to summarise key points about the study that will be added to an evidence table at the next stage of the process. **It is important that you complete this section as fully as possible, and include actual data from the study wherever relevant.**

SIGN 50: A guideline developers' handbook
Notes on the use of Methodology Checklist 4: Case-control studies

The studies covered by this checklist are designed to answer questions of the type "What are the factors that caused this event?", and involve comparison of individuals with an outcome with other individuals from the same population who do not have the outcome. These studies start after the outcome of an event, and can be used to assess multiple causes of a single event. They are generally used to assess the causes of a new problem, but may also be useful for the evaluation of population based interventions such as screening.

Section 1 identifies the study, the reviewer, the guideline for which the paper is being considered as evidence, and the key question(s) it is expected to address. The reviewer is asked to consider a series of aspects of cohort study design and to make a judgement as to how well the current study meets this criterion. Each relates to an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.

Case-control studies need to be very carefully designed, and the complexity of their design is often not appreciated by investigators, leading to many poor quality studies being conducted. The questions in this checklist are designed to identify the main features that should be present in a well designed study. There are few criteria that should, alone and unsupported, lead to rejection of a study. However, a study that fails to address or report on more than one or two of the questions addressed below should almost certainly be rejected.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

1.1 *The study addresses an appropriate and clearly focused question*

Unless a clear and well defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

1.2 *The cases and controls are taken from comparable populations.*

Study participants may be selected from the target population (all individuals to which the results of the study could be applied), the source population (a defined subset of the target population from which participants are selected), or from a pool of eligible subjects (a clearly defined and counted group selected from the source population. **If the study does not include clear definitions of the source population it should be rejected.**

1.3 *The same exclusion criteria are used for both cases and controls*

All selection and exclusion criteria should be applied equally to cases and controls. Failure to do so may introduce a significant degree of bias into the results of the study.

1.4 *What percentage of each group (cases and controls) participated in the study?*

Differences between the eligible population and the participants are important, as they may influence the validity of the study. A participation rate can be calculated by dividing the number of study participants by the number of eligible subjects. It is more useful if calculated separately for cases and controls. If the participation rate is low, or there is a large difference between the two groups, the study results may well be invalid due to differences between participants and non-participants. In these circumstances, the study should be downgraded, and rejected if the differences are very large.

1.5 *Comparison is made between participants and non-participants to establish their similarities or differences*

Even if participation rates are comparable and acceptable, it is still possible that the participants selected to act as cases or controls may differ from other members of the source population in some significant way. A well conducted case-control study will look at samples of the non-participants among the source population to ensure that the participants are a truly representative sample.

1.6 *Cases are clearly defined and differentiated from controls*

The method of selection of cases is of critical importance to the validity of the study. Investigators have to be certain that cases are truly cases, but must balance this with the need to ensure that the cases admitted into the study are representative of the eligible population. **The issues involved in case selection are complex, and should ideally be evaluated by someone with a good understanding of the design of case-control studies. If the study does not comment on how cases were selected, it is probably safest to reject it as a source of evidence.**

1.7 *It is clearly established that controls are non-cases*

Just as it is important to be sure that cases are true cases, it is important to be sure that controls do not have the

outcome under investigation. Control subjects should be chosen so that information on exposure status can be obtained or assessed in a similar way to that used for the selection of cases. If the methods of control selection are not described, the study should be rejected. **If different methods of selection are used for cases and controls the study should be evaluated by someone with a good understanding of the design of case-control studies.**

1.8 *Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment*

If there is a possibility that case ascertainment can be influenced by knowledge of exposure status, assessment of any association is likely to be biased. A well conducted study should take this into account in the design of the study.

1.9 *Exposure status is measured in a standard, valid and reliable way*

The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

1.10 *The main potential confounders are identified and taken into account in the design and analysis*

Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. **A study that does not address the possibility of confounding should be rejected.**

1.11 *Confidence intervals are provided*

Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

++ All or most of the criteria have been fulfilled.

Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

\+ Some of the criteria have been fulfilled.

Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

\- Few or no criteria fulfilled
The conclusions of the study are thought likely or very likely to alter.

The code allocated here, coupled with the study type, will decide the level of evidence that this study provides.

The aim of the other questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Section 3 asks you to summarise key points about the study that will be added to an evidence table at the next stage of the process. It is important that you complete this section as fully as possible, and include actual data from the study wherever relevant.

SIGN 50: A guideline developers' handbook
Notes on the use of Methodology Checklist 5: Diagnostic studies

This checklist is designed for the evaluation of studies assessing the accuracy of specific diagnostic tests. It does **not** address questions of the usefulness of the test in practice, or how the test compares with alternatives. These and other questions addressing the relevance of the test are entirely appropriate for guideline developers to consider, but form part of the considered judgment process where developers consider their interpretation of the evidence.

Section 1 Asks a series of questions aimed at establishing the internal validity of the study under review - i.e. making sure that it has been carried out carefully, and that the conclusions represent an unbiased assessment of the accuracy and reliability of the test being evaluated. Each question covers an aspect of methodology that has been shown to make a significant difference to the reliability of a study.

For each question in this section you should use one of the following to indicate how well it has been addressed in the study:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

1.1 *The nature of the test being studied is clearly specified.*

The clinical protocol used in deciding when to use the test should be described. The rules by which observations made during the test are converted to a positive or negative result should be stated (e.g if a continuous variable is measured the threshold value should be given).

1.2 *The test is compared with an appropriate gold standard.*

In order to assess how well a new or alternative diagnostic test performs, it has to be compared with a reference standard so that the investigator has a clear idea of how effective it is at identifying cases or non-cases among the target population. The reference standard will be some form of existing test or diagnostic method whose accuracy is known within clearly defined limits. There should be an indication in the study of exactly what test was evaluated, what standard was used for comparison, and what evidence there is that the comparator is a valid one for the test under investigation.

The comparator should ideally be a "gold standard" that is accepted as giving a correct diagnosis (necessary, but not sufficient, evidence for this might include demonstrating that inter-observer variability can be assumed to be close to zero). Where a comparator other than a gold standard is used, it must be well characterised in terms of sensitivity and specificity.

In the checklist, and throughout these notes, "test" refers to the diagnostic test being evaluated. "Gold standard" refers to the standard against which the new test is being compared. **Where a gold standard exists any evaluation of a new test that does not make comparison with that standard should be rejected as evidence, unless a clear and justifiable explanation is provided as to why the gold standard was not used.** Only studies that have used a gold standard as comparator can be considered as high quality (++) evidence.

1.3 *Where no gold standard exists, a validated reference standard is used as comparator.*

If there is no applicable gold standard, the new test must be compared with an existing test of a known sensitivity and specificity. The study should justify the use of the selected comparator. The uncertainty in the diagnosis made with a non-gold standard should be taken account of in the analysis – it is not sufficient to calculate sensitivity and specificity under the assumption that the standard has provided a true diagnosis. Studies that do not use a gold standard as comparator cannot be rated as higher than moderate (+) evidence.

1.4 *Patients for testing are selected either consecutively or randomly, from a clearly defined study population.*

The critical point here is to ensure that selection of patients is not influenced by the likelihood of obtaining a particular result from the test. There should be clearly stated criteria defining which patients are part of the study population, and which are excluded.

1.5 *The test and gold standard are measured independently (blind) of each other.*

The test under investigation and the gold standard should both be applied to the same patients to allow results to be compared. Investigators carrying out each test should be blind to the results obtained from the other to ensure their evaluation of test results is not biased. The test being evaluated should normally be carried out before the gold standard. In some studies, not all patients receiving the test will also receive the gold standard. Measures must be taken to ensure that the choice of patients for testing with the gold standard is not influenced by the results of earlier tests. **Where such measures have not been taken or are deemed to be inadequate the study should be downgraded or rejected.**

1.6 *The test and gold standard are applied as close together in time as possible*

If too much time is allowed to pass between the application of the test and gold standard, the patient's condition is likely to change (particularly if an intervention has been introduced following the test result). The test and gold standard should therefore both be applied on the same day if possible, and if not the gold standard should be applied as soon as possible thereafter. Where a length of time has been allowed to pass between tests, the study should be downgraded (or rejected if the time lapse is too long to be justifiable).

1.7 *Results are reported for all patients that are entered into the study.*

Outcomes for all patients entered into the study should be reported, including any for whom test results are unavailable for any reason. Where a significant number (>20% as a guide) of patients do not have any reported results, the study should be downgraded or rejected.

1.8 *A pre-test diagnosis is made and reported.*

In order to evaluate the additional information available from a test it is necessary to know what diagnosis would have been made (and consequently what clinical action taken) in the absence of the test. This requires a pre-test diagnosis to be recorded in each trial subject.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

- ++ The study is prospective and compares the test with a **gold standard** and adequately addresses all or most other quality criteria. The conclusions of the study are thought very unlikely to alter in the light of further research.
- \+ The study is prospective and compares the test with a **validated reference standard** and adequately addresses all or most other quality criteria. The conclusions of the study are thought unlikely to alter in the light of further research.
- \- The study is retrospective, or it fails to adequately address most quality criteria. Better designed studies are likely to alter the conclusions.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.

The aim of the other questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Section 3 asks you to summarise key points about the study that will be added to an evidence table at the next stage of the process. **It is important that you complete this section as fully as possible, and include actual data from the study wherever relevant.** Not all the measures listed are likely to appear in any one study, but any that are quoted in the paper should be entered here. Likelihood ratios are particularly useful for cross-study comparisons and can be calculated using a variety of readily available calculators.

SIGN 50: A guideline developers' handbook
Notes on the use of Methodology Checklist 6: Economic Evaluations

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review - i.e. making sure that it has been carried out carefully, and that the results are likely to be reliable and useful. Each question covers an aspect of study design that is known to make a significant difference to the conclusions of a study.

For each question in this section you should use one of the following to indicate how well it has been addressed in the review:

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)
- Not reported (i.e. mentioned, but insufficient detail to allow assessment to be made)
- Not applicable.

1.1 There is a defined and answerable study question

As with clinical evaluations, a clearly defined question is essential to allow the user to assess how well the study has met its objectives or how relevant it is to the guideline recommendation to which the results might be applied. For an economic evaluation, the question should contain information on the alternatives under comparison, the viewpoint, and (ideally) the form of economic evaluation being used and the resulting decision rule.

1.2 The economic importance of the question is clear

Not all economic evaluations are equally relevant or important. A comparison between different drugs available to treat the same condition, for example, could influence the choice of drug and possibly the overall cost of treatment. A study of drug therapy versus psychotherapy, on the other hand, could have major implications for the range, type, and extent of resources required to deliver good quality health care in a specific area. A well conducted study will provide some information on how great an impact the results are likely to have on the overall economics of the area of health care to which it relates.

1.3 The choice of study design is justified

The design of the study can have a big impact on the results derived from it. It is therefore important that the study design is clearly identified, and its limitations made clear. Each study design has its own strengths and weaknesses

and each may be appropriate under different settings.

The main types of study used for economic evaluations are:

- **Economic evaluation alongside randomised controlled trial.**

In some respects this is a good model as cost and benefit data can be collected in parallel with the clinical data, and is therefore likely to be relevant and applicable. On the other hand, a number of factors are likely to make study results unrepresentative of real practice. More resources are likely to be available in a study setting than in normal practice; patient compliance may be higher than normal; there is unlikely to be scope for economies of scale; etc. The overall result is likely to be higher costs and better outcomes in the trial than are achievable once the treatment is provided on a broader basis.

- **Before and after studies.**

A "before and after study" compares costs and outcomes before the introduction of a new therapy, and after it has been provided for some time. The major problem with this type of study design is the difficulty of attributing any changes purely to the new treatment (high risk of confounding).

- Comparative studies.

Two systems are compared in these studies - one with the new intervention, and one that does not have the new intervention but is similar in all other respects. This design is often used in areas where randomised trials are impractical or unethical. The main difficulty is in finding two directly comparable locations or systems and eliminating the possibility of confounding. In some studies comparisons may be made between a real location and an economic model. In all such studies use of sensitivity analysis to assess the reliability of results is essential, and such analyses are particularly important where model comparisons have been used.

- **Modelling of routine data sets.**

For major policy issues, econometric modelling based on data sets such as mortality or health service utilisation can be used to estimate the effect of changes. The general lack of suitable data sets makes this a difficult option to apply in a UK context.

- **Secondary economic evaluations.**

In these evaluations local data is applied to the results of published studies to produce economic evaluations that can be applied in the local context. The scope for applying such methods is limited by the range of published economic studies. Again, the effective use of sensitivity analysis is an essential part of a well designed study.´

Whichever type of design is used, the study should make clear why it was chosen, and how any possible weaknesses were addressed.

1.4 *All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately*

This is a key aspect of study design. Any study that fails to adequately detail how cost information was obtained or estimated should not be used as evidence.

All costs relevant to the study have to be identified, measured, and valued. What constitutes "relevant costs" will depend on the viewpoint of the study. A study looking at the subject from the point of view of the health service, for example, will cover all treatment and related costs. A study taking a societal view will take into account additional costs such as lost working days.

Ideally, opportunity costs (i.e. the extent to which an opportunity to use resources for some other purpose has been given up) should be used and not purely financial costs. Costs are defined as any change (either increase or

decrease) in resource use as a result of the study intervention, and measured in appropriate units.
Realistically, many studies will rely on cost data. Likely sources of such data include the financial systems of service providers, scales of charges for provision of services by the private sector, and published cost studies. All sources of cost data have weaknesses, and a well conducted study will indicate how possible uncertainties or weaknesses in the data have been addressed.

1.5 T*he outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately*

This is a key aspect of study design. Any study that fails to adequately detail how outcomes were measured and (where appropriate) valued should not be used as evidence.

All outcomes should be explicitly identified and measured, even if they are not the prime focus of the study. If, for example, a comparison of two treatment programmes showed no difference in cost effectiveness in terms of life years gained between two treatments, measurement of other factors such as long-term pain or quality of life could help choose between them.

Valuation of outcomes is only required in cost benefit analysis or other types of study where it is necessary to compare costs and outcomes in commensurate units. Even in those cases, valuation is only required where none of the options is dominant (i.e. none is clearly better and cheaper, or worse and more expensive, than the others). Methods of valuation vary considerably, and where they are used, it is essential that the valuation methods are described and associated uncertainties discussed.

1.6 *If discounting of future costs and outcomes is necessary, it been performed correctly*

In many economic studies some costs or outcomes may not arise at the time of the study, but in the future. A transplant patient, for example, may be able to resume a full life following transplant but will require lifelong drug therapy and periodic follow-up visits to hospital. These future costs and benefits must be taken into account, but should be valued at a lower level than immediate costs and benefits. This is normally done through a process of discounting at a fixed rate per annum.

Take the example of the transplant patient, and assume that following surgery he is going to be permanently reliant on drugs that currently cost £20,000 per annum. Assume also that though the actual amount paid each year remains constant, the value of this amount will decline by 6% per annum. We can now calculate how much the drug will cost in each future year, based on present day values

Year	Future value	Discount factor	Present value
0	£20,000	1	£20,000
1	£20,000	0.943	£18,860
2	£20,000	0.89	£17,800
3	£20,000	0.84	£16,800
4	£20,000	0.793	£15,860

The discount factor is calculated by working out the value of £1 less the decrease in value over the year, so in year one it is 1/1.06, in year 2 it is 0.943/1.06, and so on.

Looking at the table, it is clear that working out the cost of the drugs at a fixed rate per annum will give a very different answer to one based on the discounted rate. This is a rather simplified example, but for the purposes of study evaluation it is not necessary to evaluate such calculations in detail – just to be sure that they have been done if the interventions have long term effects, and that there is some justification for the selected discount rate.

1.7 *Assumptions are made explicit and a sensitivity analysis performed*

Economic evaluation requires assumptions to be made, but if studies are to be useful to others and comparable with other work the assumptions made must be explicit. **If a study appears to make assumptions that are not identified or explained it should not be used as evidence.**

Wherever assumptions have been made, sensitivity analyses should be carried out to see what difference variations in the assumptions would make to the final outcome. Where such analyses are not included in a study, the results should be treated with great caution.

1.8 *The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes*

The decision rule specifies the basis on which a decision about the intervention will be made – e.g. the most cost effective option will be selected. The results of an economic evaluation are normally expressed as the additional cost per additional unit of outcome. If the results are presented in some other way, the study may not be a true economic evaluation but a form of cost study.

Note that this information provides a basis for decision making, but does not represent a decision in itself: the final decision (like the recommendations based on these studies) is likely to be influenced by other factors as well as the economic case.

1.9 *The results provide information of relevance to policy makers*

Study results should be presented clearly and concisely, in a way that makes it easy for decision makers to interpret the results correctly. Ideally, the limitations of the study should be discussed along with comments on its generalisability.

Section 2 relates to the overall assessment of the paper. It starts by asking a fundamental question about the nature of the study, and whether it is a true economic evaluation. If the paper is a cost study, it will be of little or no value as a source of evidence for guideline recommendations.

The following question asks you to decide how well the study meets the quality criteria overall. This should be based on your assessment of the criteria set out in Section 1, and should use the following scale:

++ **All or most** of the criteria have been fulfilled.
Those that have not been fulfilled are very unlikely to alter the conclusions or the generalisability of the study.

\+ **Some** of the criteria have been fulfilled.
Those criteria that have not been fulfilled or are not adequately described are thought unlikely to alter the conclusions or the generalisability of the study.

\- **Few or no** criteria fulfilled
The conclusions of the study are thought likely or very likely to alter.

The final question in this section asks you to consider whether the results of this study are directly applicable to the patient population that the guideline is intended to cover. If it is not, careful consideration must be given to how generalisable the study is and whether it should be considered as part of the evidence base.

Section 3 asks you to summarise key points about the study that will be added to an evidence table at the next stage of the process. It is important that you complete this section as fully as possible, and include actual data from the study wherever relevant.

APPENDIX 4
TABLES OF EVIDENCE

Table	1									
Question	**Kangaroo Position and Hypothermia in Low Birthweight Infants**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
13/id	Bergman, 2004 13 /id	RCT	_	34 NBs of 64 estimated, 18 assigned to the KC group and 13 to the control group.(18+13=31???) There are data available neither on Lubchenco classification at birth nor about IUGR (Out of 152 candidate infants: the intervention was rejected in 1, 99 could not be included because of organization issues, 3 mothers were excluded because they underwent C-section, 5 could not be included because of lack of timely information, 9 infants had an APGAR score below 6 and 1 baby was born with malformations).	Nurse Present at Birth. Use of the SCRIP score: Cardiorespiratory Stability Score for the Premature Infant (Fisher, et al: Early Hum Dev 1998; 145-53) The SCRIP score used in the study is an adapted version. There is no information on the new version validation. Data collection was difficult because all the nurses but one left during the study.	Monitoring of stabilization during the first 6 hours of life of normal infants born in the Unit by vaginal delivery, without malformations, born to HIV negative mothers. Birthweight between 1200g and 2199g with a 5 minute Apgar score of 6. Dextrose infusion is commenced and an orogastric tube is placed in all NBs 30 minutes after birth. For the KC group 24 hour skin to skin contact; mother holds the baby close to her chest in a "frog" position For the control group incubator. Duration: first 6 hours of life	Physiological Parameters: T°, RR, HR, Oxygen Saturation every 5 min in the first hour and then every 15 min. Dextrostix at 1,3 and 6 hours.	Significant effect of the KC on hypothermia.	Temperature: P 0.006	The sample size was 64 and only 34 infants could be randomized. The sample does not represent all the children born consecutively because of staff and study organization related problems. 65% of cases could not be included at birth because of administrative reasons. The remaining 35% did not meet the inclusion criteria, resulting in 23% of randomized NBs out of the 152 infants born with a birthweight between 1200 and 2199g during this period. The sample is small, apparently there are no adjustments due to baseline differences.
								Significant effect on the number of hypoglycemic episodes <2.6 mmol/	Blood glucose <2.6 mmol/L P= 0.02	
								(+ 0.5°C in KC; 8/13 of infants in incubators had hypothermia)	Sub-analysis of NBs<1800g SCRIP first 6 hours: 0.049, SCRIP at 6 hours: P<0.008 T° effect +	
ID 135/id	Kadam, 2005 135 /id	RCT	-	44 NBs in the KC group vs. 45 NBs in the control group (CG) Infants < 1800g, 5 min APGAR score 7 or more, fed with mother´s milk from the breast or by spoon, no anomalies. It is unclear how many infants are premature and how many are IUGR	HR taken every hour, measurement of axillary T°, Questionnaire 3 questions: if she feels comfortable, if the KC will be implemented at home and if her husband agrees with this approach	Kangaroo Group: KC at least an hour daily. The infant is taken back to the open incubator when not in KC. Control Group: open incubator. Mothers allocated to either group can stay with their babies. Intervention is maintained until discharge.	T°, oxygen saturation, respiratory rate, hospital length of stay, severe infections.	Fewer episodes of hypothermia in the KC group	Temperature P<0.01	34% of the infants who were healthy in the first examination developed conditions that required treatment. Gestational age data are missing. The discharge weight of 1400g reveals a high level of related undernourishment.
								Better oxygen saturation in the KC group	O2Sat P<0.01	
								Better respiratory rate in the KC group	RR P<0.01	
								There are no differences in the hospital length of stay and/or discharge weight	T° effect +	
								There is no difference in the apnea rate		Given that the KC was neither continuous nor prolonged, it is difficult to establish a direct relationship with hypothermia or oxygen saturation.
								15 NBs (34%) of the kangaroo group were reallocated to the control group because of sepsis, apnea or jaundice		

Table		2								
Question		**Kangaroo Position and Hypothermia in Low Birthweight Infants**								
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
	Cattaneo, 1998 58	RCT	+	Low Birthweight Infants: 1000 to 1999g, without malformations and who are able to eat	Measurement of axillary T°. No more information on temperature measurements	Control group: hospital routine. Incubators in Indonesia and Mexico. Cot in warm room in Ethiopia. Mothers remain hospitalized except in Mérida.	Episodes of hypothermia or hyperthermia, and of severe diseases.	90% of KMC group infants versus 60% of control group had an adequate T° at 240 minutes.	Merida T° Hypothermia RR 0.43 95% CI 0.33 0.56 P 0.00001	In one of the healthcare centers: KMC vs. no incubator
58/id										The 3 healthcare centers are heterogeneous (birthweight, gestational age, mother´s weight, age and nutrition upon eligibility) This makes the analysis difficult, especially because there are differences that individually might not be significant but which become significant when considered as a group.
								Difference in hypothermia episodes; more frequent in the CG as a consequence of the Mérida group	Hyperthermia RR 0.09 95% CI 0.01 0.72 P 0.004	
				285 eligible infants, 38% excluded: twins, malformation, mother unavailable or rejected participation. No data on gestational age or IUGR	Case history upon admission, discharge and follow-up. 2 questionnaires for the inclusion and 1 format for costs. Follow-up at 3, 10, 20 and 30 days		Exclusive breastfeeding and weight gain.	Improved overall weight gain, not significant in separate healthcare centers and only if measured after eligibility.	Overall weight outcome after being eligible : 21.3 versus 17.7 g/day P<0,01. Non significant if analyzed based on the birthweight.	
						Kangaroo mother care in eligible infants: The kangaroo care is put into practice at least 20 hours per day by the mother or another relative if necessary.	KMC acceptance and cost assessment.	More breastfeeding in the KMC group but only in Mérida		
								More breast milk production during the follow-up; however, the drop out rate among patients was 40% at the follow-up visit on day 20.		
								Decrease in costs		
								Good acceptance by mothers and healthcare providers		
									T° effect +	
										Very interesting study. Costs are included for the first time.
172 /id	Ibe, 2004	CT	+-	13 neonates (2 twin pairs, 8 mothers and 3 relatives) Infants weighing between 1200 and 1900g, GA 32 to 38 weeks at birth. Three eligible infants after one	T° taken in the axilla and forehead with a thermometer every 5 min for 24 hours	Infants are subjected to 4 hour KMC or incubator sessions, then they are crossed over until each new born receives three 4 hour KMC sessions and three 4 hour incubator sessions in 24 hours.	Temperature (hypothermia < 36.5 or hyperthermia > 37.9)	Decrease in hypothermia episodes	Risk of hypo T°: RR 0.09 95% CI 0.03 0.25	Stable "healthy" infants. KMC vs. incubators that do not work properly. It is interesting because it depicts the condition of many neonatal units in developing countries
172	Non randomized crossover, the neonate acts as his/her own control									
								Incubators in a doubtful condition and frequent black-outs.		
									T° effect +	

Table	3									
Question	**Kangaroo Position and Hypothermia in Low Birthweight Infants**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	C I or p value	Remarks
166/id	Ludington,	RCT	++	24 healthy PTAGA	AbdomenT°measurem	3 sessions per day	Hypothermia,	*T + 0.6 °C pre/KC	P<0.03	Sound trial, shows
	2004 166/id	PTP		infants in cots.		during feed-to-feed	Apnea,	*HR +8 /min pre/KC		advantages of KMC
	RCT of KC			Randomized to the	RR, HR and O2sat	intervals	bradycardia,	*O2Sa -1	P<0.01	regarding thermal
Cardiorespiratory				KC group (11) and	continuous		periodic breathing	Neither apnea nor		regulation; additional
and thermal				to the Control Group	monitoring,	Similar sessions in		bradycardia in any	P<0.01	finding: periodic
effects on healthy				(13) in 33 to 35	pletismography for	both groups except		*Periodic breathing		breathing no longer
preterm infants				weeks of GA prior	apnea evaluation	that in the control		present during the pre		present during KMC
				to discharge		group (CG) they are		and post tests in both		
						not done in KP but in		groups.	T° effect +	
						the incubator		In the test: periodic breathing present in		
								the CG and absent in the KC group		
177	Ludington-	RCT	++	29 infants	Electronic	3 sessions a day	Foot T° as a cold	T°+ 0.9 in the KC	Delta T-	Interesting trial,
	Hoe, 2000	PTP		randomized to the	measurement T° foot	during feed-to-feed	induced stress	infant´s foot	difference in	especially because it
	177 /id			KC group (16) and	and abdomen	intervals	indicator	compared to pre and	kangaroo-control	shows the mother´s
				to the control group	Mother´s chest			post test, and control	(ANOVA with	chest temperature
				(13), 26 to 35	temperature during	Similar sessions in	Mother´s chest	+homeothermia for	repeated	increase until it reaches
				weeks of GA in	KP in the KC group	both groups except	temperature and	the mother´s chest	*KC group P	a neutral T° which
				incubator, PTAGA,		that in the control	infant´s abdomen	during KC more than	0,01; F=7.4	enables the mother to be
				neither apneas nor		group they are not	temperature	during pre and post	*Pretest/KC	in homeothermia with her
				bradycardias	Incubator T°	done in KP but in the	during KC	test	F=8.15 P 0.01	baby.
				present, without		incubator		Incubator T° range in	Postest/KC	Incubator T° range due
				oxygen delivery,				the control group	F=6.15 P 0.02	to door opening at
				weighing over					*F 5.55 P 0.004	feeding times.
				1000g upon					T° effect +	
17/id	Ludington	RCT	+	RCT22 infants 32/36	Electronic	3 sessions per day	T°	T° + 0.6	T° effect +	
	1994 17/id	PTP		weeks of GA, AGA, 5	thermometer,	during feed-to-feed	HR	HR increase		
				minute Apgar score of	abdomen T°	intervals	O2Sat	- O2Sat de		
	KC/ Research			7 or more, over 34			periodic breathing,			
	results and practice			weeks upon eligibility,		Identical sessions in	apneas			
	implications and			thermal regulation, with		both groups, 1	Deep Sleep	Twice as much		
	guidelines			neither oxygen		group in KC and the		deeper sleep		
				delivery nor treatment	Continuous monitor	CG in incubator.	Activities	Decrease of activities and shorter time		
				no anomalies, being				to accomplish a shorter deep sleep.		
				fed every 3 hours.						
175	(Bauer,	PTP	--	22 stable PTAGA	Rectal probe, foot	3 sessions: 1 hour	Rectal and	Rectal T° + 0.2	P<0.001	
	1997 175			infants with a	electrode, measured	after feeding in the	peripheral (foot)			
				birthweight of <	on abdomen	incubator during 60				
				1500g subjected to		min, an hour in KP		Peripheral T° +0.6	P<0.001	
				KC in the first week	Foot and thympanic	and again an hour in	Oxygen consumptio	Similar HR and		
				of life	Mask to measure	the incubator with		oxygen consumption		
					oxygen consumption	gavage feeding				

Table	4									
Question	**Kangaroo Position and Hypothermia in Low Birthweight Infants**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
81/id	Acolet, 1989 81 /id	RCT	--	14 very low birthweight infants, 5 with BPD but only 2 with oxygen supply using a cannula	T° measured on the back	10 min session followed by another 10 min session (5 min interval for stabilization after manipulation)	hypothermia, bradycardia hypoxemia	Only temperature was studied for 3 VLBW infants, no difference between groups	No differences at all	There is no risk of cold induced stress in the KP, but the sample is small (3 infants)
					O2Sat				T° effect ±	
					HR continuous recording					
				KP (60°) or prone (control), at random	Measured every 30 sec during the 10 min session					
149/id	Blaymore Bier, 1996 149 /id	RCT	-	50 PT <1500g whose mothers want to breastfeed. Stable premature infant, no need of oxygen supply with positive pressure	Electronic thermometer, measures of axillary T°	One 10 min observation session in KP or 10 min holding the infant (dressed) in the arms, sessions are repeated for a maximum of 10 days	O2Sat,RR, HR, T°, milk production and breastfeeding duration	More O2Sat in KP with fewer desaturation episodes <90	P<0.01	Observation periods are too short
									P<0.05	
								There is no difference in milk production while mothers are hospitalized but upon discharge higher number of mothers breastfeeding in the KC group	P<0.01	
					Measures of expressed milk				T° effect ±	
						Telephone follow-up at 1, 3 and 6 months (breastfeeding)		50% of mothers in the KC group were breastfeeding at 1 month follow-up versus 11% in the control group		
								NO differences in T° and HR		
130/id	Bohnhorst, 2004 130 /id	PTP	--	22 premature NBs of less than 32 weeks of GA and less than 36 weeks of post-conceptional age, without ventilation support, no malformations and no secondary apneas	Digital thermometer, rectal T° measured every 5 min from the onset of the first session.	three 2 hour sessions: one in the incubator, then in KP (30 degrees), afterwards in the incubator again but with higher temperature	Apneas, bradycardia and T°	Stable T° during the KP as other parameters	P<0.02	The increase in temperature does not account for bradycardia and hypoxemia episodes.
					Respiratory movements, nasal air flow, HR, continuous O2 saturation			Bradycardia plus desaturation is a little higher in the KP		
									T° effect ±	*"Combined" episodes have no clinical relevance.
										*They are unstable premature infants who could not be eligible for KC
139/id	Bosque, 1995 139	PTP of repeated measures	+-	8 infants with a birthweight over 1250g, without a tube, AGA, no drugs and with mothers willing to breastfeed them	Abdomen T° measurements	Session of 8 hours per day: 4 hours in KP and then 4 hours in incubator. 6 days a week, during 3 weeks	Apneas, bradycardia and hypoxemia	Apneas, HR, RR, O2Sat identical in both groups	p<0.03	What relation is there between this slight T° decrease and the infant not wearing a cap?
					Continuous monitoring. Observation of the behaviour every 10 min during sessions				P<0.02	
								Less total sleep time in KP	Effect –	
							T°	Temperature a little lower: -0.3	non significant	

Table 4

Question

Kangaroo Position and Hypothermia in Low Birthweight Infants

ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
81/id	Acolet, 1989 81 /id	RCT	--	14 very low birthweight infants, 5 with BPD but only 2 with oxygen supply using a cannula KP (60°) or prone (control), at random	T° measured on the back O2Sat HR continuous recording Measured every 30 sec during the 10 min session	10 min session followed by another 10 min session (5 min interval for stabilization after manipulation)	hypothermia, bradycardia hypoxemia	Only temperature was studied for 3 VLBW infants, no difference between groups	No differences at all T° effect ±	There is no risk of cold induced stress in the KP, but the sample is small (3 infants)
149/id	Blaymore Bier, 1996 149 /id	RCT	-	50 PT <1500g whose mothers want to breastfeed. Stable premature infant, no need of oxygen supply with positive pressure	Electronic thermometer, measures of axillary T° Measures of expressed milk	One 10 min observation session in KP or 10 min holding the infant (dressed) in the arms, sessions are repeated for a maximum of 10 days Telephone follow-up at 1, 3 and 6 months (breastfeeding)	O2Sat,RR, HR, T°, milk production and breastfeeding duration	More O2Sat in KP with fewer desaturation episodes <90 There is no difference in milk production while mothers are hospitalized but upon discharge higher number of mothers breastfeeding in the KC group 50% of mothers in the KC group were breastfeeding at 1 month follow-up versus 11% in the control group NO differences in T° and HR	P<0.01 P<0.05 P<0.01 T° effect ±	Observation periods are too short
130/id	Bohnhorst, 2004 130 /id	PTP	--	22 premature NBs of less than 32 weeks of GA and less than 36 weeks of post-conceptional age, without ventilation support, no malformations and no secondary apneas	Digital thermometer, rectal T° measured every 5 min from the onset of the first session. Respiratory movements, nasal air flow, HR, continuous O2 saturation	three 2 hour sessions: one in the incubator, then in KP (30 degrees), afterwards in the incubator again but with higher temperature	Apneas, bradycardia and T° hypoxemia	Stable T° during the KP as other parameters Bradycardia plus desaturation is a little higher in the KP	P<0.02 T° effect ±	The increase in temperature does not account for bradycardia and hypoxemia episodes. "Combined" episodes have no clinical relevance.
139/id	Bosque, 1995 139 /id	PTP of repeated measures	+-	8 infants with a birthweight over 1250g, without a tube, AGA, no drugs and with mothers willing to breastfeed them	Abdomen T° measurements Continuous monitoring. Observation of the behaviour every 10 min during sessions	Session of 8 hours per day: 4 hours in KP and then 4 hours in incubator. 6 days a week, during 3 weeks	Apneas, bradycardia and hypoxemia T°	Apneas, HR, RR, O2Sat identical in both groups Less total sleep time in KP Temperature a little lower: -0.3	p<0.03 P<0.02 Effect – non significant	"They are unstable premature infants who could not be eligible for KC What relation is there between this slight T° decrease and the infant not wearing a cap?

Table	6									
Question	**Kangaroo Position and Hypothermia in Low Birthweight Infants**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
392/id	Bauer, 1998. Effects of gestational age and postnatal age on body temperature, oxygen consumption, and activity during early skin to skin contact betw een preterm infants of 25-30 w eek and their mothers	Prospective clinical trial Pre and post test study	+-	27 premature infants in their first w eek of life meeting these criteria: spontaneous breathing, AGA birthw eight, no apneas in the last 24 hours or stable apneas. Eligible in the morning, measures are taken in the afternoon	Rectal T° monitoring every single minute w ith a sensor introduced up to 2 cm deep, mother´s T° and air T° del aire under the blanket that covers the baby in kangaroo position. HR and O2Sat monitoring every single minute Activity evaluated by an observer based on Brueck´s modified scale Oxygen consumption measured w ith a mask and calorimeter (system developed by the authors). All measures are taken again 7 days later if the baby´s condition is satisfactory	Rectal temperature measurement, oxygen consumption (indirect calorimetry) and infant´s degree of activity an hour before the KP w hile in the incubator, an hour in KP during and after an hour in the incubator.	Temperature, oxygen consumption and infant´s activity during kangaroo position in the first w eek of life	T° changes in the first w eek of life in relation to the GA: T° loss in infants of 25-27 w eeks of age (especially during the transfer in KP) T° gain in NBs of 28-30 w eeks (0.3°) No effect of GA during w eek 2, T° increases in all infants in kangaroo position by 0.2° KP had no effect upon RR, HR and O2 saturation More sleep during the KP in all infants as of w eek 2 No changes in oxygen consumption that increases w ith the postnatal age	P=0.0027	

Table	7								
Question	**Kangaroo Position and Gastroesophageal Reflux in Low Birthweight Infants**								
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
126/id	Orenstein, 1990 126 /id	Randomized Cross The infant is his/her own control		100 infants younger than 6 months of age with GER documented by PHmetry in 90 of them with GER of over 10% During the same period, 57 infants were not included because there were not enough beds or the investigator did not have time	PH probe placed the eve before the test. Apple juice (AJ) feeding overnight until 4:30 when a baby bottle (2ml/cm) is given. The study starts at 7:30 when AJ is administered, measurements are made during 3 hours. At 10:30 a baby bottle is given and then at 1:30 PM apple juice and another 3 hour measurement. Esophageal biopsy at the end of the study (97 infants) Measured in the postprandial period (2 h) and fasting period (1 h)	Randomization at the onset of measurements in flat prone or 30° prone position	Episodes of PH<4, number of GER episodes, number of episodes longer than 5 min, number of longer episodes de episodios. Postprandial and fasting periods.	The number of reflux episodes are reduced by raising the infant´s head and the number of GER episodes longer than 5 min after the administration of apple juice These results are not significant if only the 90 infants previously studied are considered	7.5 ±0.7 versus 5.9 ± 0.5 p < 0.05 1.4 ± 0.1 versus 1.2 ± 0.1 p < 0.05 Effect of head raising in prone 30° + position	It is uncertain whether apple juice is identical to formula milk or maternal breast milk. Is it difficult to extrapolate it?
128/id	Tobin, 1997 128 /id	Randomized cross-over for the position but not for the raising of the head. The infant is his/her own control		24 infants at term, at least 4 days after birth and less than 5 months of age, with clinical report of GER. 60 infants were included but those with less than 5% of GER were excluded. Due to technical problems (36) the randomization envelope was replaced for the next	48 hour PH monitoring with a probe	Randomization with 24 possibilities in 4 position sequences: Prone, supine, left lateral decubitus LLD, right lateral decubitus RLD (4*3*2) First 24 hours lying down in horizontal position, then the same sequence of positions but raised 30° during another 24 hours (non randomization) Measurement every 3 hours	Time with and without GER, number of episodes, number of episodes longer than 5 min, duration of the longer episode, GER overall rate	Raised Position: only a trend to have fewer GER episodes and fewer episodes longer than 5 min GER is significantly less important in the prone and LLD positions than in the supine and RLD positions, and in the prone versus all the other positions. An average of the data in flat and 30° positions was made for these measurements.	6.3±0.5 vs 5.1 ±0.5 P<0.09 1.3 ± 0.1 vs 1 ±0.1 P<0.08 GER index (prone y LLD): F=11.27, df=3.134 p<0.001 GER episodes longer than 5 min (prone and LLD): :F=4.94; df=3.134 p<0.003 Longer GER episodes (prone and LLD): :F=6.93; df=3.134 p<0.001 GER episodes (only prone): F=4.18; df=3.134 p<0.007	This study shows the benefit of the prone position but there is only a trend as per the position raised to 30°. However, moderately sick infants were included (GER 5% or more) and only the position was randomized, not the head raising.

Table	8									
Question	**Kangaroo Position and Gastroesophageal Reflux in Low Birthweight Infants**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	C l or p value	Remarks
122/id				18 premature babies of at least 7 days of life, with enteral feeding of at least 150 ml/kg, 25-32 weeks GA, weight average 480-1750g	PH monitoring during 24 hours in 3 positions: prone, RLD, LLD	Randomization among the 6 possibilities of position sequences, 8 hour measurements in each position.	Time with and without GER, number of episodes, number of episodes longer than 5 min, duration of the longer episode, GER overall rate	GER was significantly less important in the prone and left lateral positions	Prone position more effective than the LLD position (0.001; both more effective than the RLD	For GER prevention, the prone position seems to be the best. By analogy, it corresponds to the kangaroo position
		Cross-over								
	Acolet, 1999 122 /id				Infants with a GER less than 5% were not taken into account. The 11 infants treated with Cisapride or caffeine like drugs were not excluded in spite of the effect on GER; however, each infant was his/her own control					
								* diminishes the number of reflux	P<0.001	
						Varied food		*diminishes severity of episodes	P<0.002	
								*diminishes GER overall rate	P<0.001	
94/id		EOD		77 neonatal units, premature babies	Questionnaires submitted to units; 78% replies	Questions about GER of premature infants managed in Neonatal Units	% GER in less than 34 weeks; diagnostic method: clinical, PHmetry, treatment	22% of the premature infants of less than 34 weeks diagnosed with GER, PHmetry is used in 32%	Many variations by units	GER was perceived as common in these premature infants in these 77 neonatal units of the United Kingdom
	Dhillon, 2004 94 /id									
								Position treatment (prone or LLD) 98% and body tilting (96%), and medicines.		
77/id				23 premature infants with a birthweight of less than	Open incubator with a mechanical modification of positions.	3 groups of measurements: (1) in 23 infants saturation in the horizontal position and raised to 10°, 20° 30° and 45°; and the HR, RR and BP in horizontal position and raised at 45°, (2) in 10 infants, gastric emptying in horizontal position and raised to 45° and (3) in 6 infants weight gain in horizontal position and raised to 45°	Vital variables, oxygen saturation, weight gain, gastric residue	Better results are observed in prone position at 45°:	Difference 45° – 0°	
		PTP								
		non randomized crossover			The infant is secured in prone position			*better oxygenation parameters	Oxygenation 13.5mnHg; 95% CI 11.4 – 15.7 P<0.01	
					Group of 23 infants, assessment of vital signs every 30 seconds in each evaluated angle: 0°, 10°, 20°,30°, and 45° The infant remains in each position for 10 min.			*decrease of heart and respiratory rates;	RR 8.4 95% CI 6.8 – 10 P<0.01	
	Dellagrammatica s, 1991 77 /id								HR 4.17 95% CI 3.2 – 5.2 P<0.01	
								*no effect on blood pressure;		
					Group of 10 infants					
					Assessment of gastric emptying at 10 days of life. Residue 30 min after food intake at 0° and after food intake at 45°			Better gastric emptying	6.1; 95% CI 2.5 – 9.6 P<0.01	
					Group of 6 infants: weekly weight gain weeks 3-5, infants fed with formula milk and 180 cc/kg/day. 2 sequences: 10° 45° 10° or 45° 10° 45° No data on randomization					

Table	9					
Question	**Kangaroo Position and Apnea of Prematurity**					
ID	Author	Type of Study	Population	Effect	Remarks	
184/id	Osborn, 2000 184 /id	Meta-analysis	Preterm infants	-	Meta-analysis, kinetic stimulation is not useful to treat apnea of prematurity	
180/id	Henderson-Smart, 2002 180 /id	Meta-analysis	Preterm infants	-	Meta-analysis, kinetic stimulation is not useful to prevent apnea of prematurity	
2/id	Osborn, 2000 2 /id	Meta-analysis	Preterm infants	-	Teophylline is better than the kinetic stimulation to prevent apnea of prematurity	

Table	10									
Question	**Kangaroo Position and Apnea of Prematurity**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	Clor p value	Remarks
74/id	Sloan, 1994 74 /id	RCT	+-	8 KP, 147 Control Infar <2000g, able to be fed by orogastric tube at least 50% of the daily ration and with weight stabilization for 3 days, stable T° for at least 24 hours. Exclusion of twins Half are IUGR	The following is measured: growth, initial hospitalization and rehospitalization length of stay, breastfeeding and disease rate during follow -up at 1, 1.5, 2, 3, 4, 5 and 6 months.	Half the initial sample and the largest (34-35 weeks) remain with half Term SGA. Those in the KMC hold their babies in KP but there are no data on duration, infants of the control group are in a cot or incubator.	Eligible at around 13 days. One third of the sample dies after eligibility and before discharge similarly in both groups. Decrease to almost half of the More kangaroo care infants sleep with their mothers vs. more control mothers leave their babies in the cot.	Reports fewer apneas in the KP in the cohort followed up to 6 months Less morbidity in the first 6 months Fewer respiratory infections and severe infections Fewer costs although the KC group remained hospitalized 2 more days than the control group (p<0.05	p<0.007 once differences are controlled before eligibility	Of the 603 infants weighing less than 2000g, 282 are excluded (47%) 130 die (22%), 101 are twins and other causes. No data about the 130 that die, they could be the smaller infants. 320 are randomized:140 to the KP group and 160 to the control group. 193 infants are discharged from hospital, if the remaining 107 died, the mortality is 367 out of the 603 infants with a birthweight of less
ID 135/id	{Kadam, 2005 135 /id}	RCT	-	44 NBs in the KC group vs. 45 in the control group (CG) Infants < 1800g, 5 min APGAR score of 7 or more, fed with mother´s milk from the breast or by spoon, no anomalies. The proportion of preterm and IUGR is unclear	HR taken every hour, measurement of axillary T°, Questionnaire 3 questions: if she feels comfortable, if the KC will be implemented at home and if her husband agrees with this approach	Kangaroo Group: KC at least an hour daily. The infant is taken back to the open incubator when not in KC. Control Group: open incubator. Mothers assigned to either group can stay with their babies. Maintained like this until discharge	T°, oxygen saturation, RR, hospital length of stay, severe infections.	*Fewer episodes of hypothermia in the KC group *Better O2 saturation *Better RR *There are no differences in the hospital length of stay and/or discharge weight *There is no difference in the apnea rate *15 NBs (34%) of the kangaroo group were reassigned to the control group because of sepsis, apnea or jaundice	Temperature P<0.01 O2Sat P<0.01 RR P<0.01	34% of the infants who were healthy in the first examination developed conditions that required treatment. Data on gestational age are missing. The discharge weight of 1400g reveals a high level of related undernourishment. Given that the KC was neither continuous nor prolonged, it is difficult to establish a direct relationship with hypothermia or oxygen saturation

Table	11									
Question	**Kangaroo Position and Apnea of Prematurity**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
17/id	Ludington 2004	RCT	++	24 healthy PTA GA infants in cots. Randomized to the KC group (11) and to the Control Group (13) in 33 to 35 weeks of GA prior to discharge	T° measured on abdom	3 sessions per day during feed-to-feed intervals	Hypothermia, apnea, bradycardia, periodic breathing	*T + 0.6 °C pre/KC	P<0.03	Sound trial, shows advantages of KMC regarding thermal regulation; as an additional finding: periodic breathing no longer present during KMC
		PTP						*HR +8 /min pre/KMC		
					RR, HR and O2sat continuous monitoring, pletismography for apnea evaluation			*O2Sa -1	P<0.01	
Cardiorespiratory and thermal effects on healthy preterm infants								Neither apnea nor bradycardia present in either group	P<0.01	
						Similar sessions in both groups except that in the control group they are not done in KP but in the incubator		*Periodic breathing present during the pre and post tests in both groups and during the test in control group, but absent during KP in the KC group		
129/id		PTP	-	22 preterm NBs of less than 32 weeks of GA and less than 36 weeks of post-conceptional age, without ventilation support, no malformations and no secondary apneas	Digital thermometer, rectal T° measured every 2 hours from the onset of the first session.	Three 2 hour sessions: one in the incubator, then in KP (30 degrees), afterwards in the incubator again.	Apneas longer than 20 sec without differences among central apena and obstructive apnea, bradycardia and hypoxemia T	T° + 0.4 in KP	T°: P<0.05	Interesting study. No apnea episodes present. Bradycardia episodes with hypoxemia cannot be accounted for
		with blind						higher RR and HR in KP but clinically non significant (HR:150:156:153)	HR:150:156:153 p 0.01 and 0.05	
	Bohnhorst, 2001 129 /id				Respiratory movements, nasal air flow, HR, continuous O2 saturation			Lower O2Sat in KC but clinically non significant (<0.5%)	Bradycardia with hypoxemia 1.5/2.8/1.5 p 0.05 before and during P	Infants are very immature with a median of 29 weeks of gestational age. Definition of cardiorespiratory stability is missing to initiate KC
								Increased episodes of bradycardia plus hypoxemia in KC (1.5/2.8/1.5)		Cannot be extrapolated to settings where the kangaroo care is not offered to unstable infants
68/id		PTP	++	20 preterm infants and their parents	Questionnaire, *Respitrace Monitoring PT Monitoring System* that enables to detect differences among central apneas, mixed apneas and obstructive apneas	4 episodes with three 1 hour session sequence: pre KMC, KMC and post KMC. Comparison of results among sessions and infants	Behaviour of the infant and physiological stability (RR, HR, bradycardia and apnea episodes), parental stress, attitute towards the infant and acceptance of the KMC	No apneas during the KC		
	Non randomized			<37 weeks post concep (26-37), <1500g, 5 min Apgar over 6, stability during the last 48 hours				No differences in Saturation, RR and HR.		
	Messmer, 1997 68 /id							Quieter sleep during KC in relation to the pre and post test. The first episode effect is stronger.	Sleep p<0.01	
								No difference shown in mothers´ stress		

Table	12									
Question	**Kangaroo Position and Apnea of Prematurity**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
81/id	Acolet, 1989 81 /id	RCT	--	14 very low birthw eight infants, 5 w ith BPD but only 2 w ith oxygen supply using a cannula	T° measured on the back	10 min session follow ed by another 10 min session (5 min interval for stabilization after manipulation)	hypothermia, bradycardia hypoxemia	Only temperature w as studied for 3 VLBW infants, no difference betw een groups	No differences	There is no risk of cold induced stress in the KP, but the sample is small (3 infants studied)
					O2Sat					
					HR continuous recording				T° effect ±	
					Measured every 30 sec during the 10 min session			No apneas during the 20 min intervention		
				KP (60°) or prone (control), at random						
153/id		EOD	+-	8 very low birthw eight preterm infants	Rectal T° measured before and after KC	An hour session in KC at random in the morning or in the afternoon. An infant received 3 sessions, 6 received 2 sessions and 1 received one	Apneas, bradycardia and T° hypoxemia	Stable rectal T°	Effect	Eligibility criteria definition is missing.
	de Leeuw R., 1991 153 /id				Continuous recording of the HR, RR, O2 saturation			No differences in breathing patterns nor apnea episodes.	T° ±	
				(<1200g and < 30 w eeks), 7 w ith CPAP, 4 w ith oxygen supplementation, but "stable"	Normal breathing rhythm evaluation			Slight increase of bradycardias, non significant		
					Assessment of the behaviour by 2 independent observers			No differences in O2Sat and behaviour		
166/id		RCT	+	RCT 22 infants 32-36 w eeks of GA, AGA, 5 minute Apgar score of 7 or more, over 34 w eeks upon eligibility, thermal regulation, w ith neither oxygen delivery nor treatment, no anomalies, being fed every 3 hours	Electronic thermometer, T° measured on the abdomen	3 sessions per day during feed-to-feed intervals	T°	T° + 0.6	Effect +	
	Ludington 1994	PTP					HR	HR increase		
	KC/ Research Results and Practice Implications and Guidelines						O2Sat	- O2Sat de		
							periodic breathing, apneas			
					Continuous monitor	Identical sessions in both groups, 1 group in KC and the CG in incubator.	Deep Sleep	Tw ice as much deeper sleep		
							Activities	Decrease of activities and deeper sleep accomplished in shorter time.		
145/id		PTP		20 <32 WGA (average: 29 w eeks), <1600g, postnatal age: 5-62 days, spontaneous breathing w ithout oxygen supply	Cardiorespiratory system stability SCRIP score of the preterm infant (non validated)	1 episode of three 2 hour sessions each: 2 hours pre KC, 2h during KC and 2 hours post KC	RR (apneas and periodic breathing) ,HR (less than 80, 80 to 100, more than 100), Saturation (cutoff at 80 and 90)	Seven infants in KC clearly show ed (marked) more stabilization w ith <apneas, <periodic breathing, <desaturation and <bradycardia and 6 infants in KC got w orse	No significant differences in KC w hen based on the SCRIP score (non validated). Unclear data	No absolute values nor variations, it is not know n w hat a SCRIPT 1.78 corresponds to in HR compared to 2.
	Fischer, 1998 145 /id				Electrodes on the infant´s back in KC to monitor apneas and breathing					
					Continuous monitoring during the 6 hour period			Difference betw een sex, boys < stable than girls		

Table 13

Question **Kangaroo Position and Apnea of Prematurity**

ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
162/id	Tornhage, 1999 162 /id	Descriptive		17 preterm infants (P=28 weeks 24-30), <30 WGA,	T° and arterial blood gases measured at the onset and an hour later, continuous recording of HR, TcPO2 and pCO2.	At least 1 hour in KP on the third day of life (0-7). During KC 8 infants were fed by NG tube.	Apneas, hypoxemia, bradycardia	A single episode of apnea on??? 17 preterm infants at the time of the second sample. KC was never interrupted by impairment of the position. At 30 min, 16 infants were sleeping quietly and 1 was drowsy.	No comparison	
79/id	Heimler, 1992 79 /id	PTP randomized position at the onset		14 healthy preterm infants with clinical apneas, <36 WGA, 830-2290 g. Neither BPD nor enteral feeding.	Overnight monitoring during 12 hours with neumogram 2 consecutive days, once in prone and the other in supine position.	Two overnight 12 hour sessions in each studied position. During supine position, infants remain an hour in prone position after feeding to improve gas removal and prevent aspiration.	Apnea: without breathing as of 6 seconds	More central apnea density in supine than in prone position	p<0.01	Authors think that supine position results in an increased resistance to breathe and more diaphragmatic fatigue.
							Apneas density			
							Bradycardia if HR<100 during 5 seconds or longer	More periodic breathing (increase by 77%)	p<0.015	
							Periodic breathing	No difference in RR nor HR		
					Apneas and saturation were measured in 10 infants with nasal air flow and oximetry. It is emphasized that the nape and the neck should never be in flexion, either in prone or supine position		Central apnea: no more movements, no nasal air flow . Instructive apnea: no more flow with movements, no saturation drop longer than 5 seconds.Mixed apnea:	More apneas in postprandial period when the infant is in supine rather than prone position.		
							Desaturation: <87.5% for longer than 10 sec	No differences in obstructive apneas in both positions, neither in severity nor duration.		

Table	14									
Question	**Kangaroo Position and Apnea of Prematuro**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
118/id		PTP		35 preterm infants identified with apneas and bradycardia. Average age 29 weeks (25-33) and postnatal age 15 (3-49). 94% with xantines	Polygraph monitoring of prone and supine positions: nasal air flow , respiratory effort, EKG, and oxygen saturation were measured	Randomized onset, each infant is studied for 2 hours in average (between 1 and 4) after a meal in both positions the same day and only once	Apnea = period of 20 seconds or more during which breathing stops or is markedly reduced with HR<100 or O2Sat<90 or both	More central or mixed apneas in supine than in prone position, besides, they are more severe: bradycardia and hypoxemia	Matched paired analysis in mixed apneas:	Prone position seems to be definitely better than supine position in apnea in these immature infants
	randomized crossover								Desaturation duration: p=0.03	
	Kurlak, 1994 118 /id						Obstructive Apnea= respiratory effort or Mixed Apnea in which both occur in any order			
									Bradycardia: p=0.02	
									Duration of the bradycardia p=0.0003	
143/id		EOD		13 preterm infants <32 weeks, <1500g, postnatal age <60 days	Continuous monitoring of 4 infants with chest electrodes (no contact with the father´s skin) and 9 children with electrodes on the back.	1 episode of three 2 hour sessions each: 2 hours pre KC, 2h during KC and 2 hours post KC	Apnea and periodic breathing	Apneas could not be recorded due to the interference of parent´s breathing. Even more in the case of electrodes on the chest. It is advisable to use electrodes on the infant´s back during the kangaroo position to simultaneously monitor HR and oxygen saturation	Descriptive study	
	Sontheimer, 1995 143 /id									

Table	15									
Question	**Kangaroo Position and Neuro-Psychomotor Development**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
154/id	Ludington, 1992 Hashemi Argote Medellín and Rey	Descriptive study		11 healthy preterm infants >34 weeks, in the first 17 hours after birth	Infants HR and RR was continuously monitored as well as infant T° (central) and father T° (chest skin). Minute-to-minute measurements. Surveillance of the infant´s and father´s behaviour	Two hour session in kangaroo position against the father´s chest	Minute-to-minute recording of the RR, HR, O2Sat, abdominal T°, finger T°, father´s T° and father´s behaviour	All the physiological variables were within normal ranges although 5 infants showed hypothermia when being held against the father´s skin. 65% had a quiet sleep. Parents were watchful in about 65% of cases		
159/id	Ludington, 1990 159/id	Pre post-test		8 preterm infants 34-36 WGA, 1475-2765g	HR recording and behaviour monitoring (ABSS) before, during and after the test and post-test intervention	Three hour session in kangaroo position	Infant´s behaviour Heart rate	Infants in the KP spend longer hours of quiet sleep, with less activity. Longer Q-S interval during kangaroo position The HR increases with the activity		
137/id	Ohgi, 2002 137 /id	Historical control study		26 infants in the KMC group and 27 in the historical control group with an average GA and similar weights that were admitted in the NICU Exclusion criteria: weight from 1500 to 2100g, no multiple pregnancy, neither cardiac nor neurological malformations.	Performance of *NBAS (Neonatal Behavioral Assesment Scale)* at 40 weeks, *Bailey* at 6 and 12 months of corrected age and *ITQ (Carrey Infant Temperament Questionnaire)* at 6 and 12 months. Test of *HOME* at 6 and 12 months of age. The follow up is the same in both groups since it had already been implemented for all LBW infants even before the introduction of the KMC.	KC starts on the first day and if the infant tolerates it, it is implemented till discharge. First sessions last 20-30 min and then 1-2 hours during a.m. and p.m. visits. Comfortable chairs, the mother can sleep with her baby in KP. In KP breastfeeding is encouraged. Control Group: management only in incubators without carrying infants in the arms. Breastfeeding is encouraged once the infant is no longer in the incubator.	Infant´s behaviour at 40 weeks and 12 months of corrected age. Mental and psychomotor development at 6 and 12 months and surroundings.	Better behaviour in the KMC group at 40 weeks: Orientation (auditive and visual) Mood regulation (irritability) Bayley at 6 and 12 months: no difference at 6 months, however the difference is noticeable at 12 months: *Mental score* higher The *psicomotor score* tends to be higher Behaviour of the infant at 6 months of age *(ITQ test)* Difference in mood and intensity at 6 months, no differences at 12 months No difference in the HOME test at 6 or 12		

Table 15

Question **Kangaroo Position and Neuro-Psychomotor Development**

ID	Author	Typeof Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
154/id	Ludington, 1992 Hashemi Argote Medellín and Rey	Descriptive study		11 healthy preterm infants >34 weeks, in the first 17 hours after birth	Infants HR and RR was continuously monitored as well as infant T° (central) and father T° (chest skin). Minute-to-minute measurements.	Two hour session in kangaroo position against the father´s chest	Minute-to-minute recording of the RR, HR, O2Sat, abdominal T°, finger T°, father´s T° and father´s behaviour	All the physiological variables were within normal ranges although 5 infants showed hypothermia when being held against the father´s skin.		
					Surveillance of the infant´s and father´s behaviour			65% had a quiet sleep. Parents were watchful in about 65% of cases		
159/id	Ludington, 1990 159/id	Pre post-test		8 preterm infants 34-36 WGA, 1475-2765g	HR recording and behaviour monitoring (ABSS) before, during and after the test and post-test intervention	Three hour session in kangaroo position	Infant´s behaviour	Infants in the KP spend longer hours of quiet sleep, with less activity.		
								Longer Q-S interval during kangaroo position		
							Heart rate	The HR increases with the activity		
137/id	Ohgi, 2002 137 /id	Historical control study		26 infants in the KMC group and 27 in the historical control group with an average GA and similar weights that were admitted in the NICU Exclusion criteria: weight from 1500 to 2100g, no multiple pregnancy, neither cardiac nor neurological malformations.	Performance of *NBAS (Neonatal Behavioral Assesment Scale)* at 40 weeks, *Bailey* at 6 and 12 months of corrected age and *ITQ (Carrey Infant Temperament Questionnaire*) at 6 and 12 months. Test of *HOME* at 6 and 12 months of age. The follow up is the same in both groups since it had already been implemented for all LBW infants even before the introduction of the KMC.	KC starts on the first day and if the infant tolerates it, it is implemented till discharge. First sessions last 20-30 min and then 1-2 hours during a.m. and p.m. visits. Comfortable chairs, the mother can sleep with her baby in KP. In KP breastfeeding is encouraged. Control Group: management only in incubators without carrying infants in the arms. Breastfeeding is encouraged once the infant is no longer in the incubator.	Infant´s behaviour at 40 weeks and 12 months of corrected age. Mental and psychomotor development at 6 and 12 months and surroundings.	Better behaviour in the KMC group at 40 weeks: Orientation (auditive and visual) Mood regulation (irritability) Bayley at 6 and 12 months: no difference at 6 months, how ever the difference is noticeable at 12 months: *Mental score* higher The *psicomotor score* tends to be higher Behaviour of the infant at 6 months of age *(ITQ test)* Difference in mood and intensity at 6 months, no differences at 12 months No difference in the HOME test at 6 or 12		

Table	17									
Question	**Kangaroo Position and Neuro-Psychomotor Development**									
ID / Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
392/id		+-	27 preterm infants in their first week of age meeting the following criteria: spontaneous breathing, weight, AGA, no apneas in the latest 24 hours, or stable apneas. Eligibility is decided in the morning, measures are taken in the afternoon.	Rectal T° monitoring every single minute with a sensor introduced up to 2 cm deep, mother´s T° and air T° under the blanket that covers the baby in kangaroo position.	Rectal temperature measurement, oxygen consumption (indirect calorimetry) and infant´s degree of activity an hour before the KP while in the incubator, an hour in KP during and after staying in the incubator for an hour.	Temperature, oxygen consumption and infant´s activity during kangaroo position in the first week of life	T° changes in the first week of life in relation to the GA:	P=0.0027	
Bauer, 1998. Effects of gestational age and postnatal age on body temperature, oxygen consumption, and activity during early skin-to-skin contact between preterm infants of 25-30 week and their mothers	Prospective clinical trial								
	Pre and post test						T° loss in infants of 25-27 weeks of age (especially during the transfer in KP)		
				HR and O2Sat monitoring every single minute			T° gain in NBs of 28-30 weeks (0.3°)		
				Activity evaluated by an observer based on Brueck´s modified scale			No effect of GA during week 2, T° increases in all infants by 0.2° during kangaroo position.		
				Oxygen consumption measured with a mask and a calorimeter (system developed by the authors). All measures are taken again 7 days later if the baby´s condition is satisfactory.			KP had no effect upon RR, HR and O2 saturation.		
							More sleep during the KP in all infants as of week 2.		
							No changes in oxygen consumption that increases with the postnatal age.		
166/id	EAC ?? crossed	+	RCT 22 infants 32-36 weeks of GA, AGA, 5 minute Apgar score of 7 or more, over 34 weeks upon eligibility, thermal regulation, with neither oxygen delivery nor treatment, no anomalies, being fed every 3 hours.	Electronic thermometer, T° measured on the abdomen	3 sessions per day during feed-to-feed intervals	T°	T° + 0.6	Effect +	
						HR	HR increase		
						O2Sat	- O2Sat de		
Ludington, 1994						periodic breathing, apneas			
				Continuous monitor	Identical sessions in both groups, 1 group in KC and the CG in incubator.	Deep Sleep	Twice as much deeper sleep		
KC/ Research results and practice implications and guidelines						Activities	Decrease of activities and shorter time to accomplish a deep sleep.		

Table	18									
Question	**Kangaroo Position and Neuro-Psychomotor Development**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
543/id		RCT	-	Out of 71 infants, 28 are analyzed based on data, 14 in each group.	Direct observation and videomonitoring of mothers in the kangaroo group.	Pretest: Incubator 2-3 hours in prone position or cot, tilted as a nest.	32 EEG and polysomnography variables to obtain a description of the physiological dream. Some of the variables were visual, others based on computer generated data. The pretest period was compared to the test period. Blind analysis of all the visual records.	Decrease of arousal episodes during quiet sleep (QS) and decrease of REM sleep periods	Regression analysis controlling all the variables that might confound results.	Light intensity during KP was high in comparison to that of the pretest, so the light made no contribution to the improvement of quiet sleep, the quality of this dream even decreased, showing the effect of light on the sleep quality of the preterm infant.
	Ludington, 2006 PEDIATRICS Vol 117, N°5, e909-e923			Randomization according to 5 variables to get balance: sex, gestational age, severity of the disease (scale of neurobiological risk: NRS) age and weight at eligibility.	EEG and polysomnography variables durante the session before and after feeding in both groups. Sound and light were measured before the start of each session and then every 5 min. The infant´s abdominal temperature was monitored.	Then, feeding of both groups, either in the incubator or in KP. Duration of gavage feeding or VO of 2-3 hours		Light intensity was controlled since in 4 subjects this was a more important factor than the kangaroo position when considering the quality of quiet sleep.	Statistically significant results in relation to the number of episodes of arousal during quiet and REM sleep.	
	Neurophysiologic Assesment of neonatal sleep organization: Preliminary results of a RCT of skin contact with preterm infants.			Inclusion criteria at birth: Apgar > 6, GA > 28 weeks and weight over 1000 g. Without encephalopathy, IVH > 2, and no painful procedure and no sedation for more than 12 hours. Post conceptional age > 32 weeks.		Test: incubator or cot for the CG, without the mother´s presence.			1. Inadequate control of the effect modification (in the model confusion is confounded by interaction).	
						In the kangaroo group the mother is asked not to disturb her baby if apparently asleep during the session				
						KP in direct skin-to-skin contact only with the diaper, mother on a 40° inclined chair, intimacy preserved with a room divider			2. Levels of significance unadjusted by multiple analyses (temporary versus definite)	

Kangaroo Position and Hypothermia in Low Birthweight Infants

ID	Question Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
176/id	Tessier, 2003 176/id	RCT	+	431 infants, <1801 g, randomized (the study consisted of four strata, the sample includes the first three) 21 die during the first year, 2 mothers did not hold their babies, 7 Griffiths were made too late, 3 babies developed blindness and deafness, 62 mothers dropped off, 336 babies were left, 183 to KG and 153 to CG, <2000 g.	Measurements in KP and control groups at 3, 6, 9 and 12 months of corrected age: growth (weight, length, HC). Feeding (BF or formula milk or mixed) Neuro (INFA NIB test) Psychomotor Development (Griffiths test) and Morbidity (N° visits, antibiotics, rehospitalization)	Control Group: In hospital follow-up since eligibility till discharge and continues up to 12 months of corrected age, the same day as the KC group but in the afternoon. Kangaroo Group: Discharge in KP 24 hours/day with daily ambulatory follow-up and then weekly until 12 months of corrected age. Breastfeeding promotion, educational talks and evaluations carried out in both groups.	Duration of neonatal hospitalization, age and weight at discharge, morbidity (rehospitalization, days of readmission, use of antibiotics, n° of visits) up to 12 months of corrected age, somatic growth in the different cut-off dates, neurological examination at 3, 6, 9 and 12 months and psychomotor development examination at 6 and 12 months with Griffiths test.	Better psychomotor development in the KC group. There is a trend in the KC group when the infant spends some time in the NICU. There is a kangaroo effect when studying the group with a transient neurological examination at 6 months There is a triple interaction when the kangaroo effect is measured in the KC group that was in the NICU and underwent a transient neurological examination at 6 months. KMC seems to have a stronger effect in those infants who were more fragile at birth (admitted to the NICU) and who had a more difficult neurological development during the first year of life (transient neurological examination at 6 months) The triple interaction seems to be stronger in 2 subscales: performance and personal, social	P<0,02 P<0,06 P<0,05 P<0,02 P<0,01	Both groups are comparable. There is a difference in the hospital stay, especially in the group weighing <1500 g due to the early discharge in the KC group and a sex difference: more girls in the control group. Also there were more twins in the KC group. The results were controlled by this difference in sex.

Table		21								
Question		**Kangaroo Position and Neuro-Psychomotor Development**								
ID	Author	Type of	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
132/id				73 KC infants (53 Hosp B and 20 Hosp A), 73 controls (Hosp. A)	CRIB was used to classify infants as having a low or a high medical risk in the first 12 hours of life.	Intervention in the Hosp. A and then B: Kangaroo position at least 1 hour each day for at least 14 days	At 32 weeks in the KC group: monitoring of quiet sleep, REM (active) sleep, sleep waking transition with closed eyes, half awake, totally awake, agitated. The infant was monitored while being fed.	At 37 weeks there is an improvement in the mother-child interaction, especially in the low risk CRIB group. Mothers watch and touch their babies more and they get more adapted to their signs, infants are more alert with fewer gaze aversions.	MANOVA for interactions	Lineal regression model (hierarchical) with a low goodness of fit. It would be better to evaluate the association than reporting the explained variability.
		Study of 2 cohorts with individual matching		Matched pairs based on GA, birthweight, ICH < grade 2, no neonatal asphixia, wed mothers, parents with the same level of education, same income rate	Pretest: observation at 32 weeks during 4 hours sleep of the infant. This observation is repeated at 37 weeks	Skin-to-skin direct contact position. No changes were made in the neonatal unit regarding sound or lighting.			P<0.001 for the overall kangaroo effect p<0.05 for the CRIB effect	
	Feldman, Pediatrics 2002							At 37 weeks maternal perception of the infant using the BDI and NPI	Overall effect of KP: 0.001	
				Identical twins in both groups,	Monitor the infant until 37 weeks in the hospital and then examine at 3 months at home and at 6 months of corrected age in the visit to check development.		Mother-child interaction at 37 weeks and at 6 months			
				Eligibility at 31-33 PCA without ventilation but can get oxygen supply or have KT		Control group: Routine care in the incubator for the CG but not detailed	Emotion, reactivity and arousal modulation regulation at 3 months	Less depression and perception of the infant as more normal	Also with the CRIB p<0.01	
					At 37 weeks videotaping without guidance of the mother with her baby in the hospital during 10 min. Blind coding using the Mother Infant Coding System that outlines mother´s (positive, gaze, touch, vocalization) and infant´s attitudes (alertness status, gaze aversion). Plus 2 questionnaires (BDI or Beck Depresion Inventory) and NPI Neonatal Parental Inventory)		Mother´s perception about the infant at 37 weeks and maternal depression	However, the effect is really significant in the low risk group, not in the high risk group	Post-hoc comparisons	
								At 3 months:		
							Parents family environment and infant´s behaviour at 3 months	Better maternal family environment in the KC group	MANOVA test P<0.01	
							Mental and psychomotor development of the infant at 6 months of corrected age	Better paternal family environment	P<0.05	
								No differences with the CRIB		
							Shared care between the mother and infant and sustained examination of the baby at 6 months	Infant behaviour with the ICQ, neither effect nor interaction with the CRIB		
								At 6 months:		
								Better Overall Bailey Score in the KC group (5 points/100 higher)	P<0.01	
									P<0.05	

ID	Author	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
				Use of the *Parenting Stress Index PDI* (it is not mentioned when it is used exactly)		Parental stress and feeling of competence and satisfaction; mother-infant interaction; father-infant interaction and mother-father-infant triad. Microanalysis of the family triad behaviour: gazes, affect, proximity and touch.	**Effect with *CRIB:* higher risk babies have a greater likelihood of having a slower overall psychomotor development.**		
								P<0.01	
				Use of the *PCSC o Parental Competence and Satisfaction Scale* (it is not mentioned when it is used exactly)			**Overall effect of the intervention and the *CRIB***		
							Kangaroo position has a greater effect especially in the high risk group, resulting in a motor development improvement.		
								P<0.01	
				Measurement of emotion, alertness and reactivity of the infant at 3 months with the *BRP (Behavior Response Paradigm)*			**Cognitive development is better in the KC group, controlling the maternal or paternal family environment.**	P<0.01	
								P<0.05	
							Mother-infant interaction at 6 months Overall effect that is not modified by the *CRIB* showing a higher sensitivity in kangaroo mothers		
				At 3 months observers blind to the intervention visit the home, the mother and father are present, use of *HOME* with a questionnaire: the *ICQ or Infant Characteristic Questionnaire* completed by mothers and fathers separately.					
								2 hierarchical regression models to explain the MDI and	
							Explanation of the mental and psychomotor development at 6 months *MDI:* independent effect of the *CRIB*, of the infant´s degree of the alertness at 37 weeks, to the maternal low depression and high sensitivity at 6 months. KC accounts for 5% in comparison with the other variables	MDI: All the variables predict 27% of the MDI	
				Also filming without guidance: 5 min mother-child, 5min father-child and then 5min mother-father-child					
							PDI: independent effect of the mother´s attitude at 37 weeks, especially regarding touch, depression and maternal environment at 3 months.	PDI: All the variables predict 26% of the PDI	
				At 6 months, use of the Bailey II with both of its indexes: MDI mental development and PDI psychomotor development. Mother-infant interaction was filmed face to face during 5 min when it was blindly coded with the coding interactive behaviour that measures maternal sensitivity and the social participation of the infant.					
							KC accounts for 4% in comparison with the other variables.		
				10 min session of games between the mother and infant at 6 months					

Table	23										
Question	**Kangaroo Position and Neuro-Psychomotor Development**										
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
133/id		Study of 2 cohorts with individual matching		73 KC infants (53 Hosp B and 20 Hosp A), 73 controls (Hosp. A)	CRIB was used to classify infants as having a low or a high medical risk in the first 12 hours of life.	Intervention in the Hosp. A and then B: Kangaroo position at least 1 hour each day for at least 14 days	At 32 weeks in the KC group: monitoring of quiet sleep, REM (active) sleep, sleep waking transition with closed eyes, half awake, totally awake, agitated. The infant was monitored while being fed.	**No differences are observed at 32 weeks between both groups for the distribution of the types of sleep and for all the sleep-waking cycles.**		Control of confounders in the analyses, such as the medical risk during birth or a multiple birth.
				Matched pairs based on GA, birthweight, ICH < grade 2, no neonatal asphixia, wed mothers, parents with the same level of education, same income rate.	Pretest: observation at 32 weeks during 4 hours sleep of the infant. This observation is repeated at 37 weeks	Skin-to-skin direct contact position. No changes were made in the neonatal unit regarding sound or lighting.		**Type of sleep: at 37 weeks KC infants have a quieter sleep and waking during the 4 hour observation period.**	P<0.01	
	Feldman, Developmental Psychology 2002				Monitor the infant until 37 weeks in the hospital and then examine at 3 months at home and at 6 months of corrected age in the visit to check development.		Mother-child interaction at 37 weeks and at 6 months			
				Identical twins in both groups,		Control group: Routine care in the incubator for the CG, but not detailed	Emotion, reactivity and arousal modulation regulation at 3 months		P<0.05	
				Eligibility at 31-33 PCA without ventilation but can get oxygen supply or have KT	At 37 weeks videotaping without guidance of the mother with her baby in the hospital during 10 min. Blind coding using the *Mother Infant Coding System* that outlines mother´s (positive, gaze, touch, vocalization) and infant´s attitudes (alertness status, gaze aversion). Plus 2 questionnaires (BDI or Beck Depresion Inventory) and NPI Neonatal Parental Inventory)		Mother´s perception about the infant at 37 weeks and maternal depression	**Sleep-waking cycles: Better organization of the sleep-waking cycle in the KC group at 37 weeks.**	P<0.01	
							Parents family environment and infant´s behaviour at 3 months			
							Mental and psychomotor development of the infant at 6 months of corrected age	**When comparing weeks 32 and 37 including multiple birth and the *CRIB*, the progressive occurrence of a better organization of the sleep cycle is noticed, however the organization is faster in KC infants.**	P<0.05	
							Shared care between the mother and infant and sustained examination of the baby at 6 months		P<0.01	
					Use of the *Parenting Stress Index PDI* (it is not mentioned when it is used					
					Use of the *PCSC o Parental Competence and Satisfaction Scale* (it is not mentioned when it is used exactly)				P<0.05	
								Decrease of the REM sleep at 32-37 weeks with increase of the quiet waking status		

ID	Auth or	Type of Study	Qua lity	Populatio n	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
					Measurement of emotion, alertness and reactivity of the infant at 3 months w ith the *BRP (Behavior Response Paradigm*)		Parental stress and feeling of competence and satisfaction. Mother-infant interaction; father-infant interaction and mother-father-infant triad. Microanalysis of the family triad behaviour: gazes, affect, proximity and touch.	**Higher risk infants have a m ore disorganized sleep at 37 w eeks.**	P<0.05	
								Decrease of the REM sleep at 32-37 w eeks w ith sim ultaneous increase of a quiet w aking status.	P<0.05	
					At 3 months observers blind to the intervention visit the home, the mother and father are present, use of *HOME* w ith a questionnaire: the *ICQ or Infant Characteristic Questionnaire* completed by mothers and fathers separately.				P<0.01	
								At 3 months:	P<0.05	
								Overall, KC infants gaze more the stimuli w hile the CG infants have aversion gaze more frequently.		
									P<0.05	
					Filming w ithout guidance 5 min mother-child, 5min father-child and then 5min mother-father-child			KC infants have a more positive affect than CG infants.		
									P<0.01	
								Regardomg emotions regulation, the threshold for the first cry is higher in the KC group. There is a trend to last only during nociceptive stimulus. KC infants have a better management of their w aking status depending on external stimuli.		
					At 6 months, use of the *Bailey II* w ith both of its indexes: *MDI mental development* and *PDI psychomotor development*. Mother-infant interaction w as filmed face to face during 5 min w hen it w as coded w ith the*Coding Interactive Behaviour* that measures maternal sensitivity and the social participation of the infant.				P<0.01	
								Overall, at 6 months KC infants and their mothers behave w ith more shared attention and spend more time in activities and manipulations together.	P<0.01	
					10 min session of games betw een the mother and infant at 6 months			KC infants more quickly achieve a sustained exploration than the CG infants.	P<0.05	

Table	25									
Question	**Kangaroo Position and Neuro-Psychomotor Development**									
ID	Author	Type of Study	Quality	Population	Data collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
131/id	Feldman, 2003	Case control study		70 premature infants of about 32 weeks of postconceptional age (31-33), without IVH>2, no perinatal asphyxia, no genetic or metabolic disorders, no mechanical ventilation.	CRIB was used to classify infants as having a low or a high medical risk in the first 12 hours of life.	The mother accepts to carry her baby at least an hour per day during 14 consecutive days. A period when neonatal unit routine care result in the separation of the mother and the child (unclear cause) and it is during this period that infant are fed (after 34 weeks, feeding is done outside the incubator).	Vagal tone at 32-37 weeks of gestational age	Increase of the vagal tone and the heart period from 32-37 weeks.	P<0.001	Lineal regression model (hierarchical) with a low goodness of fit. It would be better to evaluate the association than reporting the explained variability.
	Development al medicine and child neurology								Time Correlation: 0.008	
					Pretest-observation before the start of the KMC for the KC group and at 32 weeks for the CG. Then, observation at 37 weeks before hospital discharge.		Observation of the infant´s status at 32-37 weeks of gestational age	Maturation of the infant´s status at 32-37 weeks		
									P<0.008	
								Longer quiet sleep periods	Time Correlation: 0.009	
							Neurodevelopment at 37 weeks	Shorter REM sleep periods.	Time Correlation: 0.005	
					HR monitoring during 10 min in quiet sleep. R waves recording and R-R interval measurement.		*CRIB*	They wake up in a quiet mood more times.	Time Correlation: 0.44	
				35 infants of the KC group and 35 of the CG matched by sex, GA, birthweight, *CRIB* and demographic characteristics of the family (mother of at least 20 years old, married to the infant´s father, and both parents with a high school level of education)				*MANOVA* with KC and sex as variables show that KC infants experience longer quiet sleep periods, shorter REM sleep periods, and they wake up in a quiet mood more times.		
					Quantification and estimation of the vagal tone to determine its index.				P<0.01	
					Data were lost regarding six 32 week infants and four 37 week infants, evenly allocated to both groups.				P<0.006	
					Monitoring of sleep during 4 hours, for 10 seconds, and status coding: quiet sleep, REM (active) sleep, sleep waking transition with closed eyes, half awake, totally awake and agitated.	In the KC group, after feeding, the mother was in charge of her baby in KP (skin-to-skin direct contact position, baby wearing only a diaper and a cap) while in the CG infants were fed in the incubator where they remained for a period not described.		At 37 weeks, NBAS test: more Neurodevelopment maturity based on the 3 items studied		
								Coupling (habituation) in relation to the medical status and vagal tone. KC accounts for 8% in comparison with the other variables.	3 Hierarchical regression models to explain the neurodevelopment at 37 weeks.	
									All variables predict 24% of the habituation or coupling	
								"Orientation" regardless of the infant´s medical risk, vagal tone and status regulation.	All variables predict 28% of the orientation	
					At 37 weeks, evaluation of the neurodevelopment status with *NBAS* that assesses 6 aspects of which 3 were evaluated in this study: "orientation", "habituation" and "range of state".			KC accounts for 7% in comparison with the other variables.		

Table	26									
Question	**Kangaroo Position and Neuro-Psychomotor Development**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
151/id				Unclear how babies are selected. Selection of a "*stratified randomized group*" of 120 infants in a sample of 348.?? Sixty of them received KMC during the first 6 months of the year and then traditional treatment during another 6 months.	*Bayley* at 6 and 12 months	KMC Group. Initiated in the unit but without accurate details, kangaroo care continues when the baby weighs at least 1500 g, depending on the sucking reflex. KMC day and night until hospital discharge and	Mental and motor development at	No difference in the averages at 6 or 12 months		More immature, with less than 31 weeks (twice as much) in the KMC with a p value=0.06
	Acosta, 2005 151 /id	Two cohorts						Differences in the results of *Bayley´s psychomotor scale with fewer "low normal" scores in the KMC group*	P<0.05	More boys than girls in the control group (10 more) p=0.06
								More "*high normal*" scores in the kangaroo group either at 6 or 12 months.	P=0.01	These differences in *Bayley´s* mental scale are no longer present when neonatal morbidity is adjusted?
				Exclusion criteria: weight lower than 2000 and less than 37 weeks of GA at birth				In the mental scale: identical results with fewer "*low*" scores in the KMC group.	P<0.02	Some results of *Bayley´s mental scale* and the nutritional status at 12 months are unclear; no longer controlled by neonatal morbidity.
								And more "*high*" scores.		
								either at 6 or 12 months of corrected age		

Table	27									
Question	**Kangaroo Position and Stabilization**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
3/id		RCT		259 LBWNB with a weight of <2000g during the study period.	There are no incubators in the control group, instead a cot heating method was used	Effect of the KMC in the first 24 hours of life for stabilization. 123 infants were randomized in the first 24 hours of life but 136 are not eligible (125 mothers are not available, 5 twin pairs and a NB with anomalies).	Demographic and socioeconomic data, daily weight, T°, episodes of severe disease, mothers´ feelings.	Quicker stabilization and lower mortality during stabilization in KP. Mothers are satisfied with the use of KMC	Stabilization: 4.6 days vs. 5.4 days. No p value	It is really a study of KMC versus no incubator. It is a study focused more on the stabilization and survival with KMC.
					A nurse collects data with the supervision of one of the researchers, data are obtained from the case history, periodic control and interview with the mother.	The KMC is a method provided to the NB in KP 24 hours and maternal breastfeeding that can be supplemented by formula milk from a cup. The KMC can be used by alternating this method with a high T° in the room. Once the baby has been stabilized (T°, HR and RR) and is able to suck, it leaves the study, it is assigned to the kangaroo care and then goes home as per the hospital´s protocol.			Mortality: 14 versus 24 die during the study p<0.05	
Worku, 2005 Kangaroo Mother Care: A Randomized Controlled Trial on Effectiveness of Early Kangaroo Mother Care for the Low Birthweight Infants in Addis Ababa, Ethiopia. [Article] 3. *Journal of Tropical Pediatrics* 51 (2):93-97				123 are eligible, 62 in the KMC group and 61 in the control group. Exclusion of twins except if one of them dies, mother´s consent to use KMC.						

ID	Author	Type of	Qu alit	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
176/id	Tessier, 2003 176/id	RCT	+	431 infants, <1801 g, randomized (the study consisted of four strata, the sample includes the first three) 21 die during the first year, 2 mothers did not hold their babies, 7 Griffiths were made too late, 3 babies developed blindness and deafness, 62 mothers dropped off, 336 babies were left, 183 to KG and 153 to CG, <2000 g.	Measurements in KP and control groups at 3, 6, 9 and 12 months of corrected age: growth (weight, length, HC). Feeding (BF or formula milk or mixed) Neuro (INFA NIB test) Psychomotor Development (Griffiths test) and Morbidity (N° visits, antibiotics, rehospitalization)	Control Group: In hospital follow - up since eligibility till discharge and continues up to 12 months of corrected age, the same day as the KC group but in the afternoon. Kangaroo Group: Discharge in KP 24 hours/day with daily ambulatory follow -up and then weekly until 12 months of corrected age. Breastfeeding promotion, educational talks and evaluations carried out in both groups.	Duration of neonatal hospitalization, age and weight at discharge, morbidity (rehospitalization, days of readmission, use of antibiotics, n° of visits) up to 12 months of corrected age, somatic growth in the different cut-off dates, neurological examination at 3, 6, 9 and 12 months and psychomotor development examination at 6 and 12 months with Griffiths test.	Better psychomotor development in the KC group. There is a trend in the KC group when the infant spends some time in the NICU. There is a kangaroo effect when studying the group with a transient neurological examination at 6 months There is a triple interaction when the kangaroo effect is measured in the KC group that was in the NICU and underwent a transient neurological examination at 6 months. KMC seems to have a stronger effect in those infants who were more fragile at birth (admitted to the NICU) and who had a more difficult neurological development during the first year of life (transient neurological examination at 6 months) The triple interaction seems to be stronger in 2 subscales: performance and personal, social	P<0,02 P<0,06 P<0,05 P<0,02 P<0,01	Both groups are comparable. There is a difference in the hospital stay, especially in the group weighing <1500 g due to the early discharge in the KC group and a sex difference: more girls in the control group. Also there were more twins in the KC group. The results were controlled by this difference in sex.

ID	Author	Type of	Qualit	Population	Data Collection Method	Intervention 1	Outcome	Effect	Cl or p value	Remarks
176/id	Tessier, 2003 176/id	RCT	+	431 infants, <1801 g, randomized (the study consisted of four strata, the sample includes the first three) 21 die during the first year, 2 mothers did not hold their babies, 7 Griffiths were made too late, 3 babies developed blindness and deafness, 62 mothers dropped off, 336 babies were left, 183 to KG and 153 to CG, <2000 g.	Measurements in KP and control groups at 3, 6, 9 and 12 months of corrected age: growth (weight, length, HC). Feeding (BF or formula milk or mixed) Neuro (INFA NIB test) Psychomotor Development (Griffiths test) and Morbidity (N° visits, antibiotics, rehospitalization)	Control Group: In hospital follow-up since eligibility till discharge and continues up to 12 months of corrected age, the same day as the KC group but in the afternoon. Kangaroo Group: Discharge in KP 24 hours/day with daily ambulatory follow-up and then weekly until 12 months of corrected age. Breastfeeding promotion, educational talks and evaluations carried out in both groups.	Duration of neonatal hospitalization, age and weight at discharge, morbidity (rehospitalization, days of readmission, use of antibiotics, n° of visits) up to 12 months of corrected age, somatic growth in the different cut-off dates, neurological examination at 3, 6, 9 and 12 months and psychomotor development examination at 6 and 12 months with Griffiths test.	Better psychomotor development in the KC group. There is a trend in the KC group when the infant spends some time in the NICU. There is a kangaroo effect when studying the group with a transient neurological examination at 6 months There is a triple interaction when the kangaroo effect is measured in the KC group that was in the NICU and underwent a transient neurological examination at 6 months. KMC seems to have a stronger effect in those infants who were more fragile at birth (admitted to the NICU) and who had a more difficult neurological development during the first year of life (transient neurological examination at 6 months) The triple interaction seems to be stronger in 2 subscales: performance and personal, social	P<0,02 P<0,06 P<0,05 P<0,02 P<0,01	Both groups are comparable. There is a difference in the hospital stay, especially in the group weighing <1500 g due to the early discharge in the KC group and a sex difference: more girls in the control group. Also there were more twins in the KC group. The results were controlled by this difference in sex.

Table 29

Question **Kangaroo Position and Stabilization**

ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
129/id	Bohnhorst, 2001 129 /id	PTP with blind analysis	-	22 preterm NBs of less than 32 weeks of GA and less than 36 weeks of post-conceptional age, without ventilation support, no malformations and no secondary apneas.	Digital thermometer, rectal T° measured every 2 hours from the onset of the first Respiratory movements, nasal air flow, HR, continuous O2 saturation	Three 2 hour sessions are performed: one in the incubator, then in KP (30°), afterwards in the incubator again.	Apneas, bradycardia and T° hypoxemia	T° + 0.4 in KP	T°: P<0.05	Interesting study. No apnea episodes present. Bradycardia episodes with hypoxemia cannot be accounted for
								Higher RR and HR in KP but clinically non significant (HR:150:156:153)	HR:150:156:153 p 0.01 and 0.05	
								Lower O2Sat in KC but clinically non significant (<0.5%)	Bradycardia with hypoxemia 1.5/2.8/1.5 p 0.05 before and during P	Infants are very immature with a median of 29 weeks of gestational age. Definition of cardiorespiratory stability is missing to initiate KC.
								Increased episodes of bradycardia plus hypoxemia in KC (1.5/2.8/1.5)		Cannot be extrapolated to settings where the kangaroo care is not offered to unstable
									T° effect +	
149/id	Blaymore Bier, 1996 149 /id	RCT	-	50 PT <1500g whose mothers want to breastfeed. Stable preterm infant, no need of oxygen supply, with positive pressure	Electronic thermometer, measures of axillary T° Measures of expressed milk.	One 10 min observation session in KP or 10 min holding the infant (dressed) in the arms, sessions are repeated for a maximum of 10 days Telephone follow-up at 1, 3 and 6 months (breastfeeding)	O2Sat,RR, HR, T°, milk production and breastfeeding duration.	More O2Sat in KP with fewer desaturation episodes <90	P<0.01	Observation periods are too short.
									P<0.05	
								There is no difference in milk production while mothers are hospitalized, but upon discharge a higher number of mothers breastfed in the KC group.		
									P<0.01	
								50% of mothers in the KC group were breastfeeding at 1 month follow-up versus 11% in the control	T° effect ±	
								NO differences in T° and HR		
130/id	Bohnhorst, 2004 130 /id	PTP	--	22 preterm NBs of less than 32 weeks of GA and less than 36 weeks of post-conceptional age, without ventilation support, no malformations and no secondary apneas	Digital thermometer, rectal T° measured every 5 min from the Respiratory movements, nasal air flow, HR, continuous O2 saturation	three 2 hour sessions: one in the incubator, then in KP (30°), afterwards in the incubator again but with higher temperature.	Apneas, bradycardia and T° hypoxemia	Stable T° during the KP as other parameters		The increase in temperature does not account for the episodes of bradycardia and hypoxemia.
								The sum of bradycardia and desaturation is a little higher in the KC group.	P<0.02	
									T° effect ±	*Combined episodes have no clinical relevance.
										*They are unstable preterm infants who could not be eligible for KC.

Table 30										
Question	**Kangaroo Position and Stabilization**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	Cl or p value	Remarks
139/id	Bosque, 1995 139 /id	PTP of repeated measures	+-	8 infants with a birthweight over 1250g, without a tube, AGA, no drugs and with mothers willing to breastfeed them.	Abdomen T° measurem Continuous monitoring. Observation of the behaviour every 10 min during sessions	Session of 8 hours/day, 4 hours in KP, then 4 hours in the incubator. 6 days a week, during 3 weeks.	Apneas, bradycardia and T° hypoxemia	Apneas, HR, RR, O2Sat identical in both groups		We might wonder whether this slight T° decrease is related to the fact that the infant is not wearing a cap
								Less total sleep time in KP	p<0.03	
								T° a little lower: -0.3	P<0.02	
									Effect – Non significant	
74/id	Sloan, 1994 74 /id	RCT	+-	8 KP, 147 Control Infan <2000g, able to be fed by orogastric tube at least 50% of the daily ration and with weight stabilization for 3 days, stable T° for at least 24 hours. Exclusion of twins Half are IUGR	The following is measured: growth, initial hospitalization and rehospitalization length of stay, breastfeeding and disease rates during follow-up at 1, 1.5, 2, 3, 4, 5 and 6 months.	Half the initial sample and of course, the largest (34-35 weeks), remain with half Term SGA. The KMC hold their babies in KP but it is not specified how long a day. Infants of the CG remain in the cot or incubator.	Eligible at around 13 days. One third of the sample dies after eligibility and before discharge similarly in both groups. Decrease to almost half of the cohort in the 4 month follow-up. More kangaroo care infants sleep with their mothers vs. more control mothers leave their babies in the cot.	Fewer apneas are reported in KP during the very incomplete follow up of 6.	p<0.007 once differences are controlled before eligibility.	Of the 603 infants weighing less than 2000g, 282 are excluded (47%); 130 die (22%), 101 are twins and other causes. No data about the 130 that die, they could be the smaller infants. 320 were randomized: 140 to the KC group and 160 to the control group. A hundred and ninety three infants are discharged from hospital, another 107 died, the mortality is 367 out of the 603 infants with a birthweight of less than 2000 g.
								Less morbidity in the first 6 months		
								Fewer respiratory infections and severe infections		
								Fewer costs although the KC group remained hospitalized 2 more days than the control group (p<0.05		
145/id	Fischer, 1998 145 /id	PTP		20 <32 WGA (average: 29 weeks), <1600g, postnatal age: 5-62 days, spontaneous breathing without oxygen supplementation	Cardiorespiratory system stability SCRIP score of the preterm infant (non validated). Electrodes on the infant´s back in KC to monitor apneas and breathing. Continuous monitoring during the 6 hour	1 episode of three 2 hour sessions each: 2 hours pre KC, 2h during KC and 2 hours post KC.	RR (apneas and periodic breathing) ,HR (less than 80, 80 to 100, more than 100), Saturation (cutoff at 80 and 90)	Seven infants in KC clearly showed (marked) more stabilization with <apneas, <periodic breathing, <desaturation and <bradycardia and 6 infants in KC got worse	No significant differences in KC when based on the *SCRIP* score (non validated). Unclear data.	Neither absolute values no value variations are reported; it is not know what a *SCRIP* score of 1.78 in HR corresponds to compared to a score of 2.
								Difference between sex, boys < stable than girls		

Table	30									
Question	**Kangaroo Position and Stabilization**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
139/id	Bosque, 1995 139 /id	PTP of repeated measures	+-	8 infants with a birthweight over 1250g, without a tube, AGA, no drugs and with mothers willing to breastfeed them.	Abdomen T° measurem Continuous monitoring. Observation of the behaviour every 10 min during sessions	Session of 8 hours/day, 4 hours in KP, then 4 hours in the incubator. 6 days a week, during 3 weeks.	Apneas, bradycardia and T° hypoxemia	Apneas, HR, RR, O2Sat identical in both groups Less total sleep time in KP T° a little lower: -0.3	 p<0.03 P<0.02 Effect – Non significant	We might wonder whether this slight T° decrease is related to the fact that the infant is not wearing a cap
74/id	Sloan, 1994 74 /id	RCT	+-	8 KP, 147 Control Infan <2000g, able to be fed by orogastric tube at least 50% of the daily ration and with weight stabilization for 3 days, stable T° for at least 24 hours. Exclusion of twins Half are IUGR	The following is measured: growth, initial hospitalization and rehospitalization length of stay, breastfeeding and disease rates during follow-up at 1, 1.5, 2, 3, 4, 5 and 6 months.	Half the initial sample and of course, the largest (34-35 weeks), remain with half Term SGA. The KMC hold their babies in KP but it is not specified how long a day. Infants of the CG remain in the cot or incubator.	Eligible at around 13 days. One third of the sample dies after eligibility and before discharge similarly in both groups. Decrease to almost half of the cohort in the 4 month follow-up. More kangaroo care infants sleep with their mothers vs. more control mothers leave their babies in the cot.	Fewer apneas are reported in KP during the very incomplete follow up of 6. Less morbidity in the first 6 months Fewer respiratory infections and severe infections Fewer costs although the KC group remained hospitalized 2 more days than the control group (p<0.05	p<0.007 once differences are controlled before eligibility.	Of the 603 infants weighing less than 2000g, 282 are excluded (47%); 130 die (22%), 101 are twins and other causes. No data about the 130 that die, they could be the smaller infants. 320 were randomized: 140 to the KC group and 160 to the control group. A hundred and ninety three infants are discharged from hospital, another 107 died, the mortality is 367 out of the 603 infants with a birthweight of less than 2000 g.
145/id	Fischer, 1998 145 /id	PTP		20 <32 WGA (average: 29 weeks), <1600g, postnatal age: 5-62 days, spontaneous breathing without oxygen supplementation	Cardiorespiratory system stability SCRIP score of the preterm infant (non validated). Electrodes on the infant´s back in KC to monitor apneas and breathing. Continuous monitoring during the 6 hour	1 episode of three 2 hour sessions each: 2 hours pre KC, 2h during KC and 2 hours post KC.	RR (apneas and periodic breathing) ,HR (less than 80, 80 to 100, more than 100), Saturation (cutoff at 80 and 90)	Seven infants in KC clearly showed (marked) more stabilization with <apneas, <periodic breathing, <desaturation and <bradycardia and 6 infants in KC got worse Difference between sex, boys < stable than girls	No significant differences in KC when based on the *SCRIP* score (non validated). Unclear data.	Neither absolute values no value variations are reported; it is not know what a *SCRIP* score of 1.78 in HR corresponds to compared to a score of 2.

Table	32									
Question	**Kangaroo Position and Stabilization**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
171/id	Schrod, 2002 171 /id	Non randomized		36 preterm infants, <35 WGA, <3000 g, no anomalies, no respiratory distress, no rescucitation at birth, no amynophylline nor caffeine.	Continuous EKG registration, respiratory impedanciometry curve, O2 saturation, brain perfusion and oxygenation by infrared spectroscopy, BP every 5 min	At least three 20 min sessions, 30° in supine, in prone, in the incubator and then in supine again. Non randomized onset. It was initiated at least 1 hour after feeding.	RR, HR, O2 Sat, brain Sat, brain Hb variations	Non randomized cross-over study, the respiratory rate significantly decreased from 10% during KC but without a decrease of oxygen saturation or	No parameters were significant	
84/id	Jenni, 1997 84 /id	RCT Crossover		12 infants, <31 GA, <1500 g, with idiopathic apneas but with spontaneous breathing	continuous monitoring of vital signs: RR, HR, Oxygen Saturation, thoracic pneumoimpedanciometry for chest movements	24 hours in horizontal position and 24 hours raised, 15% during nursing care. Randomization for the initial position. The first day, the initial position was changed every 6 hours. The second day was the contrary of the first.	Episodes of hypoxemia (less than 80%) or of bradycardia (<90/mn)	Fewer episodes of bradycardia and hypoxemia with raised vs. horizontal position of the head	Reduction of 48.5% of episodes of hypoxemia 95% CI 6.06 – 17.4 Overall reduction of these events in 24 hours with the raised head position: P<0.01	
83/id	Bhat, 2003 83 /id	CT Randomized Cross-		20 preterm infants, 32-38 WGA, 940-1940 g, ten of whom are oxygen dependent. 35 weeks of postconceptional age at the time of the study, prior to discharge	3 hours in supine and 3 hours in prone/day, during 2 days. Continous O2 Sat Monitoring and at the end of the 3 hour period. Measurement of the pulmonary functional residual capacity and of the pulmonary system resistence.	Either supine or prone positions are each maintained for 3 hours. The first position is randomized.	O2 Saturation Lung volume, Compliance Pulmonary Resistance	Prone vs. Supine * Oxygen saturation and less need of supplementary oxygen in oxygen dependent infants * Pulmonary functional residual capacity was significantly higher in prone.	O2Sat P<0.003 FRC P<0.03 Functional capacity and saturation correlation: r=0.672 P=0.0034	Interesting in relation to oxygen dependent babies. Kangaroo prone position was positive for them

Table 33

Question **Kangaroo Position and Pain & Stress**

ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
124/id	Johnston, C.C & al. 2003 Kangaroo care is effective in diminishing pain response in preterm neonates.	Cross-over study		74 preterm infants of 32-36 weeks in the first 10 days of life, no analgesics, and able to breathe without external support, in Level 2 or 3 Units in Canada.	Measurement during three 30 second long blocks after a puncture on the foot. The infant´s face is videotaped in such a way that the investigator responsible for encoding observations is not aware which group each infant corresponds to. HR and saturation continuous recording.	Initial intervention method at random. In the KC group the child is held in the arms 30 min before and 30 min after the puncture on the foot. In the CG, the infant remains in the incubator before and during the heel puncture.	Use of the *PIPP* scale that measures 3 actions: Facial, maximum HR and minimum saturation.	Lower *PIPP* in the KC group by 2 points. Identical HR and O2SatO2 in both	0.02 < P < 0.04	Analysis of repeated covariance measures based on the initiation group and site of birth. Covariable: disease severity.
1/id	Ludington, S. 2005 Skin-to-skin contact (kangaroo care) analgesia for preterm infant heel stick 2	Pre and post randomized (cross-over) test		24 "healthy" preterm infants, without oxygen supplementation, hospitalized in the NICU, were randomized. One was discharged before the end of the study. Excluded: infants with IVH, neurologic malformations or problems.	Continuous monitoring of the physiological effect resulting of the puncture related pain in KP vs. the same process in the incubator. Measurements were done in a day Measurement of: HR, RR, O2 Saturation, cry time and infant´s behaviour before, during and after the puncture.	Sequence **A**: 3 hours in KP during the interval between 2 feedings, a puncture is made on the heel for blood to be screened with dextrostix and vital signs are assessed before breastfeeding. After 3 hours in prone position in the incubator, the same procedure is performed at the end of the period and before the following feeding period. Sequence **B**: Sequence A is reversed, starting in the incubator and then in KP.	RR HR Cry	HR and cry time decreased when the puncture was made with the infant in KP vs. results in the incubator. Infants sleep more when in the KP than in the incubator.	HR:P<0.012 Cry time p<0.01	S.Ludington concludes that the KP acts like an analgesic for painful procedures performed on the preterm infant.

Table	34									
Question	**Kangaroo Position and Pain & Stress**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	Clor p value	Remarks
193/id		pptEST		16 mother-preterm infant diads, (infants of 25-33 weeks) and less than 2 days of life (2-21 days). 16 infants with *CPAP*, one assisted with a ventilator, 6 with supplementary oxygen.	Mesurements at the same time in sessions 1 and 4 in kangaroo position.	The kangaroo session is a routine and it is initiated when the infant is stable enough to tolerate the transfer from the incubator to his/her mother during an hour, the session is interrupted only if the baby becomes unstable.	Salivary cortisol concentration pre, during and post-test measured on the mother and infant. Mother´s stress and mood in the 3 cut-off points and infant´s behaviour.	Mother: Higher concentration of cortisol in the pre-test and lower in the post-test in both sessions, no differences between them.	All described differences were significant	It is difficult to interpret cortisol concentration in the saliva of infants; apparently there is not a cortisol rythmn.
					Measurement of mother´s and infant´s saliva transferred to a sample cup and frozen immediately			Using *VAS*, cortisol trend is maintained: lower in the second session in the pre-test.		
	Morelius, E. 2005. Salivary cortisol and mood and pain profiles during skin to skin care for an unselected group of mothers and infants in neonatal....???				Mother´s mood measurement with the mood and the stress scales: *VAS*			Quieter mood during the kangaroo position than before it.		*NIPS and PIPPS* seem to show that the infant is better in the KP. The mother experiments stress before the first session but with the KP improve aspects like the mood.
				3 diads were discharged from hospital before the fourth session.	Use of the pain scales *PIPP and NIPS* to evaluate pain in the infant.	During the KP session: the mother is sitting on a comfortable reclining chair, the infant is naked except for a napkin and cap and placed in skin-to-skin contact with his/her mother with covers on the back, in a dark room, with his/her father´s company.		There is no difference in the mood during session 4 though the post-test is better than the pre-test.		
					Measurements: before the KP, 30 min after the KP and 30 min after being transferred back to the incubator.			Higher HR in the pre-test on session 1 and 4, no difference between them.		The mother becomes adapted and variations are fewer for session 4.
					The same sequence is always measured: in the infant: *PIPP, NIPS* and a saliva sample is taken. Mother: *VAS, FC,* saliva saliva *mood scale*.			In infants there are variations (above and below) in cortisol levels.		
								In the first session, the HR is maximum in the pre-test and low in the KP and in the post-test. In session 4 it is lower in the KP and it increases in the post-test.		
					Many saliva samples were lost because of contamination.			The *NIPS* is lower in the KP and post-test. There is no difference between both sessions		
								NO difference in *PIPP* except in the KP and pre-test in session one.		

Table	35										
Question	**Kangaroo Position and Growth**										
ID	Author	Typeof Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks	
58/id		RCT	+	Low birthweight infants of 1000/1999 g, no malformations and able to eat	Measurement of axillary T°. No more information on temperature measurements.	Control group: hospital routine. Incubators in Indonesia and Mexico. Cot in w arm room in Ethiopia. Mothers remain hospitalized except in Mérida.	Episodes of hypothermia or hyperthermia, and of severe diseases.	*90% of KMC group infants versus 60% of control group had an adequate T° at 240 minutes	Merida T° Hypothermia RR 0.43 95% CI 0.33 0.56 P 0.00001	In one of the centres the KC is compared versus no incubator	
	Cattaneo, 1998 58 /id							*Difference in hypothermia episodes; more frequent in the CG as a consequence of the Mérida group			
					Case history upon admission, discharge and follow-up; 2 questionnaires for acceptability and a form for costs are to be filled in. Follow-up at 3, 10, 20 and 30 days.		Exclusive breastfeeding and weight gain.		Hyperthermia RR 0.09 95% CI 0.01 0.72 P 0.004	There is heterogeneity among the 3 centres (birthweight, GA, weight and age at eligibility, breastfeeding at eligibility) what makes the analysis more complex, especially because there are differences that are not significant individually and that acquire significance when analyzed as a group. Very interesting study since it assesses costs for the first time.	
				285 eligible children. 38% are excluded: twins, malformations, mother unavailable or rejected participation. It is unclear how many are preterm infants and how many are IUGR				*Improved overall weight gain, not significant if healthcare centers are analyzed individually and only if measured after eligibility.			
							KMC acceptance and cost assessment.		Weight gain results, group analysis: 21.3 versus 17.7 g/day P<0.01.		
						Kangaroo mother care in eligible infants: The kangaroo care is put into practice at least 20 hours per day by the mother or another relative if necessary.		*More breastfeeding in the KMC group but only in Mérida			
								*More breast milk production in the follow-up; however, the drop out rate among patients was 40% at the follow-up visit on day 20.			
								*Decrease in costs			
								*Good acceptance by mothers and healthcare providers.	T° effect +		

Table	36									
Question	**Kangaroo Position and Growth**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remark
85/id		RCT		74 infants, 37 in each group. Inclusion criteria: < 1600 g, 7 days, mother´s acceptance. Exclusion: twins.	They are weight with 10 g precision arm scales.	Twelve mother-infant bed Kangaroo Care Unit: KC, breastfeeding, touch stimulation, hygiene, alarm signs	Weight, episodes of disease during hospitalization, death, length of stay.	Significant differences in the assignment to groups regarding age, birthweight and weight at the time of enrolment to the study.		Of the 1 admitte 1600 g, eligible include Exclusi specifie
	Kambarami et al., 1998				Questionnaire managed by the nurse.					
						Conventional Unit: incubators with BF or formula milk		Difference in the hospital length of stay (16.6/20.7 days p<0.04) and in weight gain (20.8 g/day vs. 10.2 g/day p<0.01).		
								Non significant morbidity		
74/id		RCT	+-	KP, 147 Control Infa <2000g, able to be fed by orogastric tube at least 50% of the daily ration and with weight stabilization for 3 days, stable T° for at least 24 hours. Exclusion of twins Half are IUGR	The following is measured: growth, initial hospitalization and rehospitalization length of stay, breastfeeding and disease rates during follow-up at 1, 1.5, 2, 3, 4, 5 and 6 months.	Half the initial sample and of course, the largest (34-35 weeks), remain with half Term SGA. The KMC hold their babies in KP but it is not specified how long a day. Infants of the CG remain in the cot or incubator.	Eligible at around 13 days. One third of the sample dies after eligibility and before discharge similarly in both groups. Decrease to almost half of the cohort in the 4 month follow-up.	Fewer apneas are reported in the KMC group during the follow-up performed in the cohort until 6 moths.	p<0.007 once differences are controlled before eligibility.	Of the 6 weighir g, 282 a (47%), are twi No data die, the smaller random group a control and nin are disc hospita the mor the 603 birthwe 2000 g.
	Sloan, 1994 74 /id							Less morbidity in the first 6 months.		
							More kangaroo care infants sleep with their mothers vs. more control mothers leave their babies in the cot.	Fewer respiratory tract infections and severe infections		
								Fewer costs although the KC group remained hospitalized 2 more days than the control group (p<0.05		

Table 37

Kangaroo Position and Growth

ID	Question Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
48/id	Ramanathan, 2001. Kangaroo Mother Care in very low birth weight infants. *Indian J. Pediatr.*(11): 1019/23.	RCT		14 infants weighing less than 1500 g in each group. Hemodynamically stable (RR, HR) regulating T° in the incubator and with full enteral nutrition. IUGR in almost 80% in both groups	Weight gain is expressed per day. A questionnaire was applied to mothers on day 3 and day 7 after starting KMC. All patients were followed up at 6 weeks. No precision on the time of kangaroo exposure at home.	Kangaroo Position at least 4 hours per day in short sessions up to 3 times per day in the NICU: interpolate position with the incubator It is assumed that the kangaroo position was adopted while mother and infant were in hospital and then at home after discharge, no data available.	Breastfeeding. Hospitalization and daily weight gain. Acceptance of KMC for mothers	Better weight gain, earlier discharge and more breastfeeding 6 weeks after discharge in the kangaroo group. Mohters feel closer to their babies in the kangaroo group and think it is not a problem to hold them in the kangaroo position	Weight: 15.9 g vs. 10.6 g p<0.05 Hospital stay in days: 27.2 versus 34.6 p<0.05 **At six weeks 12/14 were in exclusive breastfeeding vs. 6/14 p<0.05**	Sample size No data on the duration of KP at home
48/id	Rojas et al., 2001	RCT		60 preterm infants (27 basic care and 33 KC) ≤32 weeks and ≤ 1500 g with minimum ventilation, CPAP or cannula, hemodynamic stability, no asphyxia, no malformation. Babies born to drug-addicted or adolescent mothers were excluded as well as infants with IUGR, sepsis or grade 3 or 4 intraventricular hemorrhage	Continuous monitoring of physiological variables, weigh on electronic scale, length and head circumference with standardized measures taken each day by the same person. A questionnaire about the problems encountered, applied after each period in kangaroo position. Comfortable and reclining chairs. Measured until the child is discharged from hospital or reaches 2000 g.	Held in the arms: basic care, child not in the incubator, held in father´s or mother´s arms, wearing a T-shirt, diaper and a cover. Kangaroo Position: 45° position, skin-to-skin on the chest, infants weighing less than 1000 g with a cap and a cover on their backs. KP offered 8 hours per day, two 4 hour sessions/day. Infants in the basic care group could also receive kangaroo care if parents wanted it.	RR, HR, T° and O2Sat before, during and after KC Weight, length and head circumference	In spite of being a RCT, basic care was initiated between 0 and 15 days while KC was initiated between 0-28 days; consequently children stayed in basic care 22±15 days or KC 15±15 days (p<0.03) Fathers hold their babies 27% in basic care and 31% in KC (non significant difference) **The kangaroo group had a larger head circumference (control group: 6.4 at discharge vs. kangaroo group 7.7 cm; P:0.01) and with a higher growth rate (0.08 in the basic care group vs. 0.1 in the kangaroo group; P: 0.05)**		The sample size was estimated in 45 infants in each group; there were fewer children than expected.

Table	38									
Question	**Kangaroo Position and Growth**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
49/id	Charpak 2001 49 /id	RCT	+	Randomization of 746 LBWI of <2001 g. 382 to the kangaroo group and 364 to the control group.	Measurements of weight, height and head circumference (HC) at eligibility, each day in the hospital for the CG and each day in the visit for the KC up to discharge for the control group and then up to 40 weeks of post conceptional age for both groups	Control Group: Follow up in the hospital, from the time of the eligibility till discharge. Then follow up until 12 months of corrected age in the same visit as that of the KC group but in the afternoon.	Length of neonatal hospital stay, age and weight at discharge, morbidity (rehospitalization, days of readmittance, use of antibiotics, number of visits) up to 40 weeks of post conceptional age and during the year of somatic growth regarding the different cut-off dates, neurologic examination at 3, 6, 9 and 12 months, and psychomotor development evaluation at 6 and 12 months.	Weight at eligibility a little lower in the KC group: 1678 vs. 1713 with more infants transferred to the NICU	p<0.01	The earlier discharge of infants in the KC group did not result in a higher risk for the baby when reaching 40 weeks of post conceptional age or at the age of one corrected year.
								No difference in mortality 11 (3.1%) versus 19 (5.5%)		
				Eligibility: stable, without treatment nor oxygen supply, coordination of suck and swallow, mother committed with the follow-up, T° regulated in the incubator	Measurements of growth (weight, length and CD), feeding (breastfeeding, formula milk, mixed), neurological (*INFANIB* test) and psychomotor (*Griffiths* test) development, morbidity (N° of visits, antibiotics, rehospitalization) in the KC and control groups at 3, 6, 9 and 12 months of corrected age.	Kangaroo Group: discharge in kangaroo position 24 hours at one day with daily and then weekly outpatient follow-up up to the 12 months of corrected age in the morning of the KC visit. Breastfeeding promotion, educational talks and evaluations were carried out in both groups.		Shorter hospital length of stay since eligibility to one year in the KC group especially for infants weighing less than 1500 g. Higher rate of visits.	P<0.05 RR 0.57 95% CI 0.17-1.18	
								More hospital acquired infections in the control group.	p<0.001	Benefits were found: more breastfeeding, less morbidity, similarly good growth in both groups with a better HC growth in the kangaroo group.
								Identical growth for weight and length, higher CD in the KC group.	p<0.014	
								Same psychomotor development at one year in both groups.		
								More breastfeeding up to 3 months of postconceptional age. Which group?	p>0.05	
								Same sequelae		

Table 39: Question: BF and DD (table translated from the textbook Biologıa de l' allaitement by M.Beaudry, S.Chiasson, J.Lauziere, 2006, Presse de L Universite du Québec,

Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
Duffy et Al 1986	Prospective Cohort		197 mother-infant dyads (low income). (<185% of the lowest level) followed up from 6 to 9 months during the Rotavirus season).	Personal or telephone interview of one of the authors with the mother twice a month. Coproscopic investigation in the 24 hours of each DD episode and before each control visit or for another cause.	Classification at birth: 1) Exclusive breastfeeding, 2) Mixed breastfeeding and 3) Formula feeding (same classification at 4 months plus breastfeeding < 4 months)	DD: more than 3 bowel movements per day during 2 days associated to clinical signs or vomiting reported by the mother...Rotavirus infection: positive bacteriology	Non specific DD risk decreases by 70% in the group with exclusive breastfeeding for more than 4 months versys the other combined groups. Ridk of the 2 breastfed groups versus the group that was never breastfed Rotavirus infection: less severe in the breastfed infants.	RR 0.29 CI 0.24-0.83 RR 0.57 CI 0.37-0.87 Effect + (protector of BF)	Adjustments for the baby's sex and ethnicity, and mother's age, schooling, occupation and marital status.
Rubin et Al 1990	Prospective Cohort		Of 500 infants, 461 were followed up at 1 month and 223 were followed up at 12 months (44% of the sample)	Postpartum interview through a questionnaire sent by mail every month, asking about the disease and type of feeding	At 13 weeks classified as: 1) predominant breastfeeding without supplementation except water and fruit juice 2) mixed feeding for 13 weeks or more with supplementation 3) breastfeeding interrupted before 13 weeks 4) never breastfed	DD def. based on the mother´s and social assistant´s reports plus case histories analyses after 2 years of age: DD diarrhea or vomiting or both for more than 48 hours VOMITING: definition besides regurgitation DIARRHEA: frequent liquid or soft stools	DD incidence decreases in 1/3 of breastfed infants versus those who were never breastfed. This effect persists more than the breastfeeding period during the whole year. Hospitalized because of lower DD in infants breastfed over 13 weeks versus those who were never breastfed	Effect +	Results adjusted by parents social and economic factors, and smoking.
Rubin et Al 1990	Prospective Cohort		Of 500 infants, 461 were followed up at 1 month and 223 were followed up at 12 months (44% of the sample)	Postpartum interview through a questionnaire sent by mail every month, asking about the disease and type of feeding	Classification regarding the length of BF versus formula feeding: 1) exclusive breastfeeding 2) BF > formula feeding. 3) BF=formula feeding 4) BF<formula feeding 5) only formula feeding Secondary grouping between breastfed versus non	DD: data provided by the mother *Presence of at least 2 of these signs during 2 to 20 days: T equal to or over 38,5° , liquid bowel movements or vomiting *At least 3 of the symptoms if the duration is not reported 3) DD diagnosis reported by the mother and provided by a consulted physician	No differences after adjusting confounders	Effect =	Adjustment by birthweight, social and economic factors, infants day care center, number of children at home and other family diseases

Table 40: Question: BF and DD (table translated from the textbook Biologi a de l' allaitement by M.Beaudry, S.Chiasson, J.Lauziere, 2006, Presse de L Universite du Québec,

Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
Wright. et Al 1989	Prospective Cohort		1022 infants followed-up during the first year, 1144 followed during the first 4 months	Respiratory diseases: the infant has deep and productive cough, wheezing, harsh voice, fatigue upon exertion Prospective: each control visit (2, 4, 6, 9 and 12) it is asked whether the infant is being breastfed. Retrospective with questionnaire to the parents at 12 and 15 months. 90% match, priority to prospective data if both are available.	Breastfeeding duration: 1) No breastfeeding or breastfeeding less than a month 2) 1 to 4 months breastfeeding 3) More than 4 months of breastfeeding	Any lower respiratory tract disease, with or without wheezing evaluated in 3 age categories: 1) 0 to <4 months 2) 4 to 6 months 3) >6 to 12 months Def. of lower respiratory tract disease: case history of acute coughing or wheezing and symptoms that cannot be accounted for by a simple nasal obstruction, acute crackles during inspiration (Croup) and positive radiologic findings. Diagnoses set up and documented by the pediatrician were the only accepted ones.	Lower respiratory tract disease with wheezing: Higher incidence in the first 4 months in breastfed infants younger than 1 month vs. breastfed infants older than 1 month. Observed trend of an effect in breastfeeding duration lower respiratory tract disease or without wheezing: no relationship with breastfeeding duration during the first year. These results suggest the importance of stratifyingbreathing with or without wheezing	Eleven times higher risk in the breastfed boys younger than 1 month that share a room and are Mexican Effect +	Results adjusted by mother´s smoking, schooling, ethnics; infant´s sex; parent´s history of lower respiratory tract disease before 16 years of age, and by the fact that other children sleep in the same room. Parents were also asked if the infant spent over 9 hours weekly with other children.
Howie et Al 1990	Prospective cohorts		674 mother-infant dyads, 618 followed-up up to 2 years and 545 examined at 7 years of age.	Interview by social workerhome visit at 2 weeks, 1, 2, 3, 4, 6, 9 ,12 15,18, 21 and 24 months using standardized forms. Retrospective evaluation of case histories	At 13 weeks classified as: 1) Predominant breastfeeding without supplementation except water and fruit juice 2) Mixed feeding for 13 weeks or more with supplementation 3) Breastfeeding	Def. of respiratory disease: during the first year rhinitis with cough and/or wheezing during 48 hours or more. Follow-up at 7 years: one or more of the following symptoms: persistent cough, wheezing or thoracic pressure at any time since birth or in the last 12 months	Plus respiratory tract disease in the first 13 weeks in infants never breastfed (37%) versus mixed feeding (24,2%) or predominant breastfeeding (25.6%). Identical but weaker effect for the respiratory disease in the weeks 40-52. In the follow-up at 7 years increased probability in infants never breastfed versus mixed feeding.	Effect +	Results adjusted by parents social and economic factors, smoking and history of parents´ respiratory tract disease.

Table	41									
Question	**Kangaroo Position and Early Discharge in Kangaroo Positi**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
6/id				1362 preterm infants, 3 clinical trials: Cattaneo, Sloan and Charpak	An almost impossible meta-analysis, the KMC is different regarding how studies are applied: Sloan does not submit data on the KP duration along the day, almost half the cohort is lost at 4 months.	It seems better to analize each paper individually (Cattaneo in hypothermia and grow th; Sloan in apneas, grow th and early discharge and Charpak in this setting)	Follow -up data are almost exclusively obtained from Charpak´s trial			Difficulty to perform the meta-analysis because of lack of trials, data and the non standardization of KMC.
		Cochrane Meta-analysis								
		RCT KMC versus Incubator								
	Conde-Agudelo, J. L. az-Rossello, and J. M. Belizan. 2000 Kangaroo mother care to reduce morbidity and mortality in low birthw eight infants.				Cattaneo: KP in hospital. No early discharge in KP, no follow -up, not systematized by chronologic age up to 30 months.					
					Charpak: Early discharge in KP up to 12 months.					
210/id		RCT		Stable LBW infants w ithout apneas nor bradycardia for at least 3 days, regulating T° in a cot, breastfed and living in safe house in the city or surrounding areas.	Randomization w hen chosen for the early discharge group vs. group discharged at 2300 g.	Early discharge group: w hen eligible, visit on day one by a community nurse, w ho w ill then be 24 available by phone, providing support during 2 months, including home visits if necessary.	Post conceptional age at discharge	Earlier discharge in the KP group	36.6 ± 1.5 versus 37.3 ± 1.6 p<0.04	
	Shapiro, C. 1995. Shortened hospital stay for low -birth-w eight infants: nuts and bolts of a nursing intervention project. *J.Obstet.Gyn ecol.Neonatal*				Psychomotor development measurement by Bailey´s and HOME test application at one year of corrected age .		Number of rehospitalizations, *Bayley´s* results	At 1 year of corrected age: NO difference in morbidity nor in *Bayley´s* result		
								Difference in the *HOME* test (acceptance of the infant´s behaviour, material to play)		
						Control Group: routine visit of a community public health nurse	*HOME*		No P provided, difference of a little over than 200 US$ per infant	
								Few er costs including: home support, visits, nurse support to the KC group		

Table		42								
Question		Follow-up and Vitamin K								
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
420/id	Prospective Cohort Mc Ninch, AW. 1991 Haemorrhagic disease of the new born in the British Isles: 2 years prospective study BMJ; 303:1105			27 patients with confirmed or probable hemorrhagic disease of the new born	Monthly survey of the British Pediatric Unit	Oral prophylaxis with vitamin K in 6 patients	Incidence of hemorrhagic disease of the new born	Reported rate of hemorrhagic disease by 100 000 live births, Overall 1.62, 8.63 without prophylaxis, 1.42 with oral prophylaxis, 0.11 with IM prophylaxis	CI 95% (0.998 to 2.24)	
487/id	Retrospective Cohort Von Kries, R. 1992. Vitamin K prophylaxis and vitamin K deficiency bleeding (VKDB) in early infancy. Acta Paediatri; 81:655			Cases of Vitamin K deficiency bleeding in infants born between 1988 and 1989 in obstetric and pediatric hospitals in Western Germany	Survey on the number of cases of late bleeding in the new born: Infants between 1 and 16 weeks Prothrombin index < 10% of normal level Return to normal level 24 hours after vitamin K injection.	55.8% of hospitals 1 mg Vitamin K IM or SC In 18.7% of hospitals an oral dose was given to all infants. Only those infants classified as high risk (preterm, IUGR, C-section or neonatal disease) received an IM dose 18.5% only one IM dosis to high risk infants	Incidence	Incidence 1/14 000 without prophylaxis 1/70 000 with a single oral dose 1/420,000 with a single IM dose 50% of intracraneal hemorrhage cases 1/30,000 with neurologic sequelae or death RR: 30.3 RRR 1 dosis vs no prophylaxis: 96.7% CI No significance difference between the oral dosis vs. parenteral.	95% CI (3.9 - 235.6)	

Table	43									
Question	**Follow-up and Vitamin K**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
429/id				Patients in the Netherlands, Germany, Australia and Switzerland between October 1992 and December 1995	Monthly survey of the British Pediatric Unit	Vitamina K prophylaxis in the Netherlands: BR: 1 mg po then 25 mcg/day until week 13 in babies with BF. AR: 1 mg IM plus same treatment.	Incidence of bleeding resulting from Vitamin K deficiency	Incidence per 100,000 inhabitants	95% CI	
		Retrospective cohort						Holland: 1.1	(0.4-2.7)	
	Cornelissen M and Coll, 1997. Prevention of Vitamin K deficiency bleeding:efficacy of different multiple oral doses schedules of vitamin K Eur J. Pediatr.156:126-130					Germany: BR: 1 mg po day 1, 4-10,28-42. AR: 0.1-0.2 mg IM day 1 then 1 mg po day 4-10,28—42		Germany 2.7	(1.8-3.8)	
						Australia: Before 1994: BR: 1 mg po day 1, 3-5.21-28. AR: 0.1 mg IM day 1 and 0.1 mg IM or 1 mg po day 3-5 and 21-28, After 1994: 1 mg IM day 1		Australia: 2.5	(1.1-4.8)	
								No reported cases for Vitamin K IM		
						Switzerland: BR: 2 mg po day 1 and 4, AR: 0.5 mg IV or IM day 1 then 2 mg po week 4-6		Switzerland: 4.7	(1.3-11.9)	
488/id				Surveys were sent to 21 pediatrics departments in Denmark twice a year for 5 years since June 1991 to February 1996	Questionnaires reporting cases of late Hemorrhagic Disease of the New born. Protocols were requested in November 1995 only.	Before 1992 Vitamin K 1 mg IM at birth	Late Hemorrhagic Disease of the New born.	Incidence per 100,000 livebirths: 4.5 before 1992		Before 1992 data are consistent with Switzerland 5.1 per 100,000 and Switzerland 7.6 per 100,000 livebirths.
		Retrospective Cohort				After 1992, 2 mg po at birth, then 1 mg po weekly when breastfeeding represents more than 50% of feeding			P< 0.01	
		Historical Comparison					Bleeding Site	No case reported after 1992		
							Concomitant Diseases			
	Noogard Hansen K, Ebbesen F " Neonatal Vitamin K prophylaxis in Denmark: three years'experience with oral experience with oral administration during the first three months of life compared with one oral administration at birth" Acta Paediatr 1996; 85:1137-113						Sequelae			15% of infants at risk (liver disease) receive the dosis intramuscularly at birth.

Table 44

Question **Kangaroo Position and Early Discharge in Kangaroo Position**

ID	Author	Study type	Quality	Population	Data Collection Method	Intervention 1	Outcomes	Effect	CI or p value	Remarks
197/id	D. Brooten, S. A RCT of early hospital discharge abd home follow up of VLBWI, NEJM 1986 Oct	RCT		Preterm <1500g at birth, 72 mothers and 79 infants (twins were included), exclusion of ICH grade 4, oxygen requirement for more than 10 weeks, surgical intervention 39 in the early discharge group and 40 in the control group.	Randomization at birth in one of the 2 groups Early discharge group: discharge preparation training in baby care at least once a week before discharge.	Control group: discharge at 2200g when the infant is able to suck adequately	Hospitalization length, age and weight at discharge, mortality, rehospitalization, serious disease, abuse.	11 left 2 days earlier, weighing 200g less and being 2 weeks younger		
						Early discharge group: Discharge when the infant regulates T° in cot, eats adequately, has an appropriate home in the town, no apneas or bradycardia in the 12 hours before discharge		No significant differences were found in the other variables at 18 month follow-up	p<0.05	
					Then visits to specialized nurse the first week, and at 9, 12 and 18 months apart from telephone acces during office hours			Difference in the initial cost of hospitalization and in the costs of further use of medical services: lower in the early discharge group.		
					14 and 11 infants are discharged in each group with apnea monitoring			Reduction in total costs including follow-up costs	p<0.01	
9/id	Brooten, S. 1991. Gennaro, H. Knapp, N. Jovene, L. Brown, and R. York. Functions of the CNS in early discharge and home follow up of very low birthweight infants 2. Clin.Nurse Spec. 5 (4):196-201	Descriptive Study		Preterm <1500g at birth, 36 mother with 39 infants (twins were included). Exclusion CIH grade 4, oxygen requirement for more than 10 weeks, surgical intervention. Randomized to early discharge vs. discharge at 2200g group	Randomization at birth in one of the 2 groups Early discharge group: discharge preparation training in baby care at least once a week before discharge.	Early discharge group: Discharge when the infant regulates T° in cot, eats adequately, has an appropriate home in the town, no apneas or bradycardia in the 12 hours before discharge	All specialized nursing activities are measured during the first 2 weeks of intervention and education in the early discharge group	68% are teaching activities		Interesting as it relates somehow to what is called hospital kangaroo adaptation where the baby is prepared for an early discharge in the kangaroo position and with breastfeeding
					Then visits to specialized nurse the first week, and at 9, 12 and 18 months apart from telephone acces during office hours					
					Telephone calls 3 times in the first 2 weeks and then once weekly for 8 w					

Table **45**

Question **Kangaroo Position and Early Discharge in Kangaroo Position**

ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
49/id	Charpak 2001 49 /id	ECA	+	746 LBWI weighing <2001g, 382 randomized to the kangaroo care group and 364 to the control group Eligibility: stable, without treatment nor oxygen supply, coordination of suck and swallow, mother committed with the follow-up, T° regulated in the incubator	Measurements of weight, height and head circumference (HC) at eligibility, each day in the hospital for the CG, and each day in the visit for the KC, up to discharge for the control group, and then up to 40 weeks of post conceptional age for both groups Measurements of growth (weight, length and CD), feeding (breastfeeding, formula milk, mixed), neurological (INFANIB test) and psychomotor (Griffiths test) development, morbidity (N° of visits, antibiotics, rehospitalization) in the KC and control groups at 3, 6, 9 and 12 months of corrected age.	Control Group. Follow-up in the hospital from eligibility till discharge. After follow-up up to 12 months of corrected age in the same visit as the KC group but in the afternoon. Kangaroo Group: discharge in kangaroo position 24 hours at one day with daily and then weekly outpatient follow-up up to the 12 months of corrected age in the morning of the KC visit. Breastfeeding promotion, educational talks and evaluations were carried out in both	Length of neonatal hospital stay, age and weight at discharge, morbidity (rehospitalization, days of readmittance, use of antibiotics, number of visits) up to 40 weeks of post conceptional age, and during the year of somatic growth regarding the different cut-off dates, neurologic examination at 3, 6, 9 and 12 months, and psychomotor development evaluation at 6 and 12 months.	Weight at eligibility a little lower in the KC group: 1678 vs. 1713 with more infants transferred to the NICU No difference in mortality 11 (3.1%) versus 19 (5.5%) Shorter hospital length of stay since eligibility to one year in the KC group especially for infants weighing less than 1500 g and higher rate of visits. More hospital acquired infections in the control group **Identical growth for weight and length, higher CD in the KC group** Same psychomotor development	p<0,01 p<0,05 RR 0,57 95%IC 0,17-1,18 p<0,001 p<0,014	The earlier discharge of infants in the KC group did not result in a higher risk for the baby neither when reaching 40 weeks of post conceptional age nor at the age of one corrected year. Benefits were found: more breastfeeding, less morbidity, similarly good growth in both groups with a better CD growth in the kangaroo

Table 46

Question **Kangaroo Position and Early Discharge in Kangaroo Position**

ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
20/id	Thompson JM, Jackson Gunn TR. 2000. *Acta paediatrica,* (11):1358-1363, 200	RCT		308 preterm infants <37 weeks breastfed Early discharge group: 140, control group: 160. 122 parents did not accept to take part in the study.	Randomization before the infant receives totally oral feeding. Early discharge group: discharge with total oral feeding without weight gain Control Group: total oral feeding with weight gain	Control group: During the nurse´s visit day, longer visits according to the needs of breastfeeding support. Early discharge group Nurse´s visit every day for 7-10 days and then available 24 hours by phone.	Breastfeeding, rehospitalization, maternal satisfaction.	Days in hospital with complete oral feeding: Early discharge 2.5 ± 2 versus control 4.4 ± 2.8 No difference in breastfeeding period. At 6 months: 36% in both groups	p<0.01	
25/id	Karan, S. 1983. Benefits of early maternal participation in care of lowbirthweight infants leading to early discharge. *J.Trop.Pediatr.* 29 (2):115-118	Descriptive study		610 LBW infants were admitted to the study during 1 year. 39% dies (especially <1500 g). Of the 309 infants weighing <1800g only No data available regarding IUGR	Exclusion criteria: clinically stable (no diseases), regulating temperature and able to suck adequately	Discharge when meeting the discharge criteria regardless the weight. Follow-up at 1 year	The type of feeding, growth per day instead of kg per day, number of infections and rehospitalizations are evaluated.	They are hospitalized 20 days in average but it is difficult to estimate the outcome since a large part of the sample was not followed up, it is not known whether they died. It seems that those infants with exclusive breastfeeding did better		79 infants returned for the follow-up but it is not mentioned when they returned. The chart seems to point out that at 4 months more than half the sample was lost and 80% at 1 year; it is unclear.
37/id	Bhutta, Z. 2004 Reducing length of stay in hospital for very lowbirthweight infants by involving mothers in a stepdown unit: an experience from Karachi BMJ 329 (7475):1151-1155,	Descriptive study, comparison of a historical cohort		509 VLBW infants <1500 g: 494 preterm infants and 140<1000 g No data regarding IUGR	First historical cohort: 1987-1994 Second cohort 1995-2001 Eligibility for discharge when the baby regulates temperature in cot, eats and gains weight. In spite of quoting KMC it seems not to use it.	Effect of the founding in 1994 of the step-down unit where the mother learns how to take care of her baby before discharge: Training in exclusive maternal breastfeeding, kangaroo mother-child pair lodged together, aparently without KMC.	Survival from birth till discharge, neonatal hospitalization length of stay, diseases during hospitalization and rehospitalization in the first month after discharge.	Low neonatal hospitalizat vs. 15.4 (SD 15.7) p<0.001 Low weight at discharge vs. 1286 (SD 220) P<0.001 Increase in survival to 83% (RR 0.69? 0.56 - 0.85) Lower GA at discharge	22.2(SD 21.7) vs. 1489 (SD 210) Survival 67% 35.3 (2.8) weeks vs. 33 (3.3) weeks at discharge	No data regarding somatic growth. No data on malnourishment upon discharge and at one month. Preterm infants of 33 weeks of postconceptional age should regulate their T° in the same way no matter whether they are in Karachi or in Bogotá.
									Does not control variables like surfactant use	

Table	47									
Question	**Kangaroo Position and Early Discharge in Kangaroo Position**									
ID	Author	Type of Study	Quality	Population	Data Collection Method	Intervention 1	Outcome	Effect	CI or p value	Remarks
135/id	Ramanathan. 2001. Kangaroo Mother Care in very low birth weight infants. *Indian J.Pediatr.* (11):1019/23.	RCT		14 infants of a weight <1500 g in each group. Hemodynamically stable (RR, HR), regulating T° in the incubator and with complete enteral feeding.	Weight gain is expressed per day. A questionnaire was submitted to mothers on day 3 and day 7 after starting KMC.	Kangaroo position at least 4 hours/day in short sessions up to 3 times per day in the NICU: interpolate position with the incubator	Breastfeeding,	In the kangaroo group, better weight gain, earlier discharge and more breastfeeding 6 weeks after discharge.	Weight: 15.9 g vs. 10.6 p<0.05	Small sample size.
							Hospital length of stay and daily weight gain.		Length of stay in days: 27.2 versus 34.6 p<0.05	No data on KP duration at home.
					All patients were followed up at 6 weeks.	It is assumed that the kangaroo position was adopted while mother and infant were in hospital and then at home after discharge, no data available		Mothers feel closer to their babies in the kangaroo group. They report having no problems when adopting the KP.	**At 6 weeks, 12/14 breastfeed exclusively vs. 6/14 p<0.05**	
				IUGR in almost 80% in both	No accuracy regarding how long KP should be implemented at home.		Acceptance of KMC for mothers			

APPENDIX 5
DISCUSSING BF AND COGNITIVE DEVELOPMENT

The question posed by the Guide is:
In preterm or low birthweight babies, is exclusive or predominant use of breastfeeding from their own mother associated with a better short, medium and long term psychomotor and/or cognitive development as compared to infants predominantly fed using formula milk?
The basic answer is:
It is unclear whether there is an association between breastfeeding and better neurological, psychomotor development and better academic performance. However, the association between breastfeeding (the mother decides to feed the infant with her own milk) and better neurological, psychological and intellectual development can be ascertained. Overall the documented effects are more significant in preterm infants than in term infants.

Running experimental studies on humans allocating subjects to breastfeeding, donor's milk or formula is ethically inappropriate. Most of the available observational studies show a positive association between breastfeeding and better psychomotor and intellectual development. Attributing these effects to human milk's nutritive and biological properties is difficult, since breastfeeding in all those studies is associated in not only to breastfeeding (by the same mother) but also to various levels of mother-child interaction (related to the breastfeeding act), more encouraging and devoted mothers (who have voluntarily decided to breastfeed). In fact, various studies and systematic reviews suggest that the positive effects of breastfeeding may be attributed to confounding factors instead of a net effect of breast milk. In any case, the evidence shows it is appropriate to encourage breastfeeding as much as possible since the point of view of the neurological and intellectual development.

An exhaustive bibliographic review has been performed, which is not included in the main body of the guide but given its general significance, it appears in the following appendix.

Bibliographic Review of the Relationship among Breast milk, Breastfeeding and Psychomotor Development:

The main source consulted was the book Biologie de l'allaitement by M. Beaudry, S. Chiasson, J. Lauziere, 2006, Presse de L Universite du Québec1, which summarizes results from various systematic reviews and includes an search update up to 2005. The search of published articles and systematic reviews to complement the main source identified some further publications.

There is significant heterogeneity in the original papers and in the systematic reviews which summarize them as to five important aspects:

a) study populations (term infants, preterm infants, IUGR, and generally a combination of these)
b) Exposure variables: exclusive breastfeeding, administration of breast milk (variants of processed breast milk versus direct breastfeeding), preterm formula, breast milk proportion (breastfeeding plus term or preterm milk bank) versus formula.

c) Duration of breastfeeding (ranging from poorly defined to weeks or months)

d) Endpoint variables: development ratios, different scales and subscales, age at which measures were taken, and

e) Study methodology and quality: a few randomized controlled studies, often post hoc assembled subgroup analyses using population samples included in randomized controlled studies seeking to answer other questions, analytical observational studies, non-controlled descriptive studies. Often there is no adequate control of the potential confounding factors: parents' educational level, degree of infant stimulation and interaction, baseline health status, etc.

As a consequence, the possible conclusions as to the general advantages of breast milk and particular advantages of breastfeeding to improve preterm infants' neurological, psychomotor and cognitive development should be treated with caution.

In 2002 Jain A et. al2 suggested eight criteria for assessing quality in studies on the association between breastfeeding and cognitive endpoints: 1. design (observational: birth cohort, historical cohort, case and control), 2. Sample size and power, 3. Study population (term, preterm), 4. Quality of nutritional data (definition of breastfeeding, timing of data collection, source of data and duration of breastfeeding), 5. Confounding factors (family's socioeconomic status and infant's stimulation), 6. Blind assessment 7. Cognitive endpoint measures (test and age of assessment) and 8. Report of raw effects or adjusted by confounding factors.

The following systematic reviews assessed satisfactory compliance with the eight quality criteria suggested by Jain et al.

Systematic reviews:

Meta-analysis by Anderson J.W. et al3

Literature from the last 30 years was reviewed. Twenty studies based in the UK and the US meeting the following criteria were selected: a) Mainly breastfed infants compared with mainly formula fed infants and b) measuring the primary effect with a validated cognitive development or performance test, which can be summarized in a single outcome and c) measures taken between infancy and adolescence.

Fourteen of these 20 studies had enough data to be included. Eleven studies have adjusted results to control confounding factors. These 11 studies involve about 10,000 children of each feeding option. All studies are observational. The different studies include term and low birthweight infants. The main conclusions are: a) Breast milk administration is associated with a small though consistent increase in cognitive development: 3.16 (95% CI 2.35-3.98) higher in breast-fed infants compared to non-breastfed infants; b) The better cognitive development is detected earlier in infancy and persists through adolescence and c) The longer the breast milk administration (more than 8 weeks) the higher the gain in cognitive development. In the low birthweight subgroup gain in cognitive scores is apparently higher: (5.18; 95% CI: 3.59-6.77).

Standardized methods (both fixed effect and randomized effect) for meta-analyses of outcomes from RCT were used to estimate the average effect. Each study used adjusted estimates to calculate effects and no meta-analysis adjusted by covariables was done. Adjustments in each study were heterogeneous since they controlled different groups with potential confounding factors.

In summary, the assertions so far are limited in terms of reliability even when conclusions suggest that breast milk administration for more than 8 weeks associates with better results in cognitive performance tests, particularly in preterm infants, since it implies a summary of results from observational studies, most of them (Lucas, et al4) involving post hoc assembled groups with significant heterogeneity in the control for confounding factors. The included studies barely meet the criteria suggested by Jain.

Systematic review: Drane DL, Logemann JA.5

Drane and Logemann published in 2000 a critical appraisal of 24 studies published between 1996 and 1998 involving children whose births occurred between 1960 and 1998. The methodological quality criteria included: endpoint is clearly defined, partial versus exclusive breastfeeding is specified and confounding factors are controlled. Nineteen studies report better cognitive development in exclusively or partially breastfed children, but in most of them the methodological quality is unsatisfactory. The most frequently absent criterion was not distinguishing between exclusive breastfeeding and mixed feeding. Only six studies stated this difference. Four out of 6 included studies showed better cognitive development in breastfed term babies (2 to 5), and a higher difference (8) in preterm babies.

The main conclusions established by the authors are:

1. Few studies meet acceptable validity criteria, which limits the possibility of a real estimation of an as sociation between feeding and cognitive development.
2. Only short-term effects of mixed or exclusive feeding are studied.
3. Studies distinguishing exclusive breastfeeding from mixed feeding show a higher difference in the Intel ligence Quotient (IQ) favoring breastfed children.
4. Four out of 6 studies meeting the 3 strict criteria found a IQ 2 to 5 points higher in term breastfed in fants and 8 points in preterm breastfed infants.

Narrative review: Reynolds, A6

In 2001 Reynolds analyzes results from 4 systematic reviews on the effect of breast milk on neurological development of both term and preterm infants. For term babies, the meta-analysis by Anderson and 3 reviews published during that time are examined: **Jacobson, Malloy and Horwood**. The first two reviews show an absence of effect as opposed to the third:

Jacobson initially showed an association between feeding duration and IQ at 4 and 11 years. This association disappears when adjusting for mother's education, parental skills and socio-economic level.

Malloy and Berendes initially studied a population with term babies receiving a soy-based commercial preparation with insufficient chlorine levels to a fault in production. No differences were found at 9 and 10 years whether they had been breastfed or not but breastfeeding duration was obtained at the age of 10, and the fact that this is very short period in the breastfed group makes results little reliable.

Horwood and Fergusson followed more than 1000 babies in New Zealand. Exclusive and partial breastfeeding are distinguished. Outcome measures include cognitive skill testing, academic achievement measures and school achievement as perceived by teachers. Results were adjusted to 11 possible confounding factors by the authors. For practical purposes, results are normalized to an average of 100 and to a SD unity of 10 for standardized tests, and an average of 3, SD 1 for teachers' assessments. After adjusting, there is an association between breastfeeding duration and a slight but significant increase of the IQ in 10 of the 12 outcome measures assessed. Babies receiving 8 or more months' breastfeeding had results with SD 0.11 to 0.30 higher than non-breastfed babies. These differences remain unaltered until the onset of adulthood, and the effect is higher with longer breastfeedings.

When repeating these analysis with exclusive breastfeeding duration, there is no change in 9 out of 12 assessed results.

These results are consistent with Anderson's. One of Horwood's academic achievement indicators was leaving school: there were 33% fewer cases before the end of secondary education in non-breastfed subjects.

At the end of this review, Reynold concludes that the effects of breastfeeding on cognitive development are not significant for preterm infants. The author believes that provided children are healthy, these differences are not clinically significant (for an individual). However, the author observes that small differences distributed over a whole population may have an important global effect on society.

Despite existing methodological concerns, the effects of breastfeeding may be more important in preterm than in term infants. Reynolds6 mentions that IQ 13 times lower were observed in low birthweight infants (< 750-1000 g) versus term controls, with a 50 to 60% risk of requiring special support at school entrance. The same author highlights a slight increase in IQ and neurological function in these children may have a significant impact.

Narrative Review Jaín D2.

In 2002 Jain executes another review of 40 studies on breastfeeding and cognitive development published between 1929 and 2001. In 68% of these studies authors sustain that breastfeeding has a positive effect on intelligence. Only two studies involving term babies meet the 8 methodological criteria applied by Jain, of which one favors and another is against breastfeeding. Jain concludes that results from rigorous studies do not favor an effect of breastfeeding on IQ

Other reviews

In 2003 Rey examines the subject (2003 Breastfeeding And Cognitive Development Acta Paediatr 92 (Suppl) 442 11-18) but this review is a result of a request by a formula manufacturer seeking to improve quality of their products, and this laboratory invites 5 nutrition experts for discussion. Methods and criteria are unaccounted for and conclusions are unclear.

Burgard in this same meeting (2003 Critical evaluation of the methodology employed in Cognitive developments trials Acta Paediatr suppl 92 (442) 6-10) presents a critical appraisal of the evaluated methods. The conclusions approximate those of Anderson's:

a) Breastfed children have 2 or 3 points in the IQ
b) Children who were breastfed 28+ weeks are 2.91 points above those breastfed 4 to 7 weeks
c) Non-breastfed children do not match those who were breastfed
d) Effects are higher in low birthweight children

Last studies published after 2003

Five new studies have been published, four involving term babies and one in very low birthweight preterm infants (< 1500g: M.M.Smith and Co Influence of breastfeeding on cognitive outcomes at age of 6-8 years: follow up of very low birth weights infants), all prospective and cohort studies.

All studies including term infants showed an association between breastfeeding and its duration with cognitive development after adjusting for confounding factors; however, none satisfies Jain's eight methodological criteria

Richards et al[7] from UK showed that breastfeeding associated positively to cognitive development by 15 years and school level attained by 26 years, in a health survey involving 1739 men and women born in 1946. The relationship remains unaltered until 53 years.

E.L.Mortensen et al.[8] report a perinatal cohorte (973: 490 men and 483 women) who are administered the Wechsler (WAIS) test when they are 27,2 years old (4,4 years) and 2280 men in Denmark's military service who were administered another intelligence test (BPP) at the age of 18,7 years (1,2 years). A positive association was observed between breastfeeding until 9 months and adult intelligence after adjusting for 13 confounding factors, including head of household's schooling and social stratum. The IQ difference between breastfed children for 9+ months and those breastfed less that 1 month was significant in the WAIS-assessed group. Scores were lower but showing the same trend in the BPP-assessed cohort.

These studies failed to address two methodological aspects: distinguishing between exclusive and partial breastfeeding and including confounding factors related to parental skills other than schooling and economic status.

P. J. Quinns et al.[9] in 3880 Australian children evaluated at 5 years, were the only ones to include a child's stimulation and parental skills measure, with four questions posed to the mother during the six-month follow-up. However, the authors made no distinction between exclusive and partial breastfeeding and did not blind the assessment. A positive association between breastfeeding duration and IQ at 5 years was observed: girls breastfed for 6+ months had 8.2 points more than non-breastfed girls and boys breastfed for 6+ months had 5.8 points more, after adjusting for confounding factors.

W.H.Oddy (Breastfeeding and Cognitive development in childhood: a prospective birth cohort study Paediatr perinat epidemiol 17(1) 81-90) included 1400 Australian children assessed at 6 and 8 years of age but did not include parental skill measures or measures addressing the stimulation received by the child. They distinguished between partial and exclusive breastfeeding. Verbal IQs were estimated with PPVY-R, showing a clearly positive effect dependent on the amount of breastfeeding received. Children who had been given milk other than their mothers' in the first 6 months had a verbal IQ lower than 3.56 after adjusting for confounding factors. The WISC3 was applied at 8 years and no differences were found between children breastfed 6+ months and those who were not breastfed.

The study by Smith10, involving low birthweight children assessed at 6-8 years, found similarly higher scores in the visual and motor integration measures in those who had received their mothers' milk. Results were adjusted using Home brief version by the authors, which makes their documents more reliable.

All these studies have their own methodological flaws, only Quinn and Smith measures parental skills and stimulation received by the child and Oddy's distinguishes between exclusive and non-exclusive breastfeeding.

2006: In a recently published study **by Geoff Der, G David Batty and Ian J Deary**[11] on the effects of breastfeeding on children's intelligence (Prospective study, analyses and meta-analyses), the obtained results do not indicate there is an effect of breastfeeding on children's future intelligence.

The objective of this study was to assess the significance of maternal intelligence and the effect of other confounding factors for a causal link between breastfeeding and children's intelligence.

The confounding factors included breastfeeding duration, gender, maternal history of smoking, maternal intelligence, maternal training, race, socioeconomic level, size of family nucleus, order of births, weight at birth, gestational age and child's personal.

The study, involving 12,686 individuals between 14 and 22 years of age when interviewed for the first time, was initiated in 1979 on to 2002 and included some of the first participants' own children.

Measures:

- Cognitive skills: Peabody individual achievement test (PIAT)
- Breastfeeding: Duration
- Child's environment: Home observation for measurement of the environment scale (HOME-SF)
- Child's demographic characteristics: Sex, age, gestational age, birthweight and labor characteristics.
- Maternal characteristics: Cognitive skills measured with the AFQT scale, schooling level, race, and socio economic stratum.

Results from this study conclude that the most important factor for children's intelligence is maternal intelligence and other factors related to maternal education, training and socioeconomic level. When the factors mentioned above are taken into account, the influence of breastfeeding is not significant. However, breastfeeding becomes significant in analyses where maternal intelligence is not considered, which could have substantially altered the results and their interpretation.

Potential mechanism of action of the effect of BF on intelligence:

Two mechanisms are postulated:

1. Effect of substances in breast milk
2. Effect of the physical contact on mother/child bonding and on parental skills.

Indirect breastfeeding effects should also be considered, such as lactating mothers with higher oxytocin and prolactin levels. These hormones have a soothing effect and stimulate mothers' nurturing. The breastfeeding-development relationship would also be modulated by intermediate variables.

In studies involving preterm babies with a weight of < 1850g Lucas[4] tries to discriminate the effect of breast milk on the mother/child interactions associated to direct breastfeeding. A group receiving mainly breast milk by gavage versus a group not receiving breast milk were compared. Babies receiving their mother's milk had higher scores in the Bayley test at 18 months and WISC-R test at 7-8 years, after adjusting for confounding (socioeconomic) factors. The women who decided not to lactate had a higher socioeconomic and educational level than the mothers who did. For women who decided to lactate but couldn't, their babies' IQ at 7-8 years was the same as those who had decided not to lactate.

Conclusion: The evidence supporting the superiority of breast milk is based on observational studies mostly consisting in post-hoc sub-analyses of controlled trials aimed at answering other questions. The identified systematic reviews summarizing results of these studies found that, despite methodological flaws, all suggest that the administration of breast milk is associated with medium and long-term better intellectual development as compared to using formula milk, and these different are more evident among preterm than term babies. Nevertheless, recent studies favor an effect of the environment and mothers' education and willingness instead of an effect of breast milk per se. Considering beneficial effects of breast milk on digestive tolerance, nutritional quality and protection against infection, the arguments to stimulate feeding preterm babies with milk from their own mother are valid.

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APPENDIX 6
VITAMIN SUPPLEMENTATION

Question: **Is there any evidence supporting the need to use fat-soluble vitamin supplementation to breast-feeding in preterm and/or low birthweight infants?**

Evidence-based Answer: **Yes. Fat-soluble vitamins supplementation should be administered regardless of the nutrition source. The choice of route and duration of Vitamin K supplementation is controversial.**

Evidence Level: **Experts' consensus, regulating agencies' recommendations. For Vitamin K, experimental studies, meta-analysis, prospective and retrospective observational studies.**

Level of consensus: **Agreement (not all participants revised this item).**

Rationale:

It is widely accepted that healthy, breast-fed term infants do not require vitamin supplementation (except for vitamin K). Breast milk is an excellent source of water-soluble vitamins and their levels reflect the mother's nutritional status (B and C). The same applies to fat-soluble vitamins A and E but not necessarily to vitamins D and K. Vitamin D deficiency may be observed in breast-fed babies who do not receive supplementation, particularly those residing in temperate and subpolar areas where maternal and neonatal exposure to the sun is scarce, or when the infant's skin is darker(ref). Deficiency is also observed in preterm infants or with liver disorders(ref).

Vitamin K is vital for liver synthesis of clotting factors (II, VII, IX and X). Given the short half life of these factors and the little capacity of the body to store vitamin K, if vitamin intake is insufficient deficiency of vitamin K-dependent clotting factors ensues, resulting in abnormal bleeding.

The term vitamin K addresses a group of three types of chemically similar fat-soluble components known as naphthoquinones. The first type (vitamin K1, phylloquinone or phytonadione) is contained in green vegetables and is the main source of vitamin K in children and adults; the second type involves vitamins K2 or menaquinones, which are synthesized by intestinal bacteria and complement the dietary source; and the third type is vitamin K3, a water-soluble synthetic compound (menadinone), which has almost twice as much the potency of the two previous types but its use in children is not authorized in the United States.

Breast milk is an insufficient source of vitamin K and vitamin K supplementation in newborn infants to prevent bleeding disease has been accepted since the 1950s. In fact, universal vitamin K supplementation has been given at birth in most high-income countries since the 1960s.
Term and preterm newborn infants are prone to hemorrhagic disease of the newborn (HDN) as a result of Vitamin K deficiency. Three types of HDN are described[1-5]:

1. Early HDN: within 24 hours). It is rare and is not prevented by neonatal vitamin K administration. It occurs almost exclusively in babies whose mothers are receiving drugs that affect maternal synthesis of vitamin K and their placental transfer: anticonvulsants, antibiotics, particularly those used to treat tuberculosis, and anticoagulants. It may be prevented by giving vitamin K to the high risk mother.
2. Classical HDN: It manifests between day 1 and day 7. It results from a low antenatal placental input, low levels in breast milk and initial intestinal sterility where vitamin K2 bacterial synthesis is not present. Formula and cow's milk contain high levels of vitamin K, so this deficiency occurs in babies with exclusive breastfeeding. Risk increases from delays in the initiation of feeding.
3. Late HDN (2-12 weeks): It occurs in babies with exclusive breastfeeding and who have not received neonatal prophylactic vitamin K, or babies with insufficient input (for example 1 or 2 doses of oral vitamin K), and/or with a disorder that reduces synthesis or absorption of vitamin K: malabsorption syndromes, prolonged diarrhea, hepatitis, cystic fibrosis and 1-antitripsine deficiency, among others. Central nervous system hemorrhages occur more frequently3;6;7 and therefore this deficiency implies a higher risk of mortality and sequelae.

The optimal type, dose, and frequency of administration of vitamin K for preventing hemorrhagic disease of the newborn (vitamin K deficiency) are controversial. The evidence available reports that administering vitamin K 0.5 to 1 mg IM (single dose) in babies with a weight 1500 g, and 0.5 mg in babies with < 1500 g, in the first six hours after birth, is virtually effective in 100% of cases for preventing classic HDN, and very close to 100% for cases of late HDN (0 incidence in the U.S. and Europe, 0.2/100,000 live births in Australia) while the incidence with oral regimens of vitamin K is higher (see table8).

	Australia[8] Rate by 100,000 newborn infants	Europe
No Vitamin K	34.4	
Konakion(R) 1 oral dose	20	
Konakion MM(R) 2 mg, 2 doses, orally		5
Konakion(R) 3 oral doses	4.1	2.6
Konakion MM(R) 2 mg, 3 doses, orally		0.44
Konakion IM(R) 1 oral dose	0.2	0.0

The preventive effect of a single injection of Vitamin K1 IM was admitted in the 1950s, and since 1960 the AAP recommends the systematic administration of a single dose of Vitamin K1 0.5 to 1 mg to all NB at birth[9]. A study Publisher by Holding in 1990[10] suggested an association between the neonatal administration of Vitamin K IM and an increase in the risk of infant cancer. Subsequently, prospective and retrospective observational studies have not confirmed such association and the scientific consensus points out that this risk is hardly any likely, and if it did, benefits would widely outweigh the risk with the prevention of HDN[11-18]. A regime containing oral Vitamin K1 2 mg at birth and then 1 mg weekly until 3 months of age in mainly breast-fed infants (more that 50% of breastmilk use) is used in Denmark, and it seems to be as effective as the IM administration of a single dose of Vitamin K1 1 mg[19]. By contrast, the American Academy of Pediatrics9 and health care agencies in Canada (http://www.rcp.gov.bc.ca/guidelines/Master.NB12.VitK.pdf) , Great Britain (http://www.ich.ucl.ac.uk/clinical_information/clinical_guidelines/cpg_guideline_00003), Australia and New Zealand (http://www.adhb.govt.nz/newborn/Guidelines/Blood/VitaminK.htm#1) among others recommend the administration of a single dose of IM Vitamin K1. They sustain this claiming that: a) evidence on the effectiveness of a single IM dose of Vitamin K1 is firm; b) cancer risk with the administration of IM vitamin K has been convincingly ruled out and c) effectiveness of different regimes of oral vitamin K1, including mycelium preparations20, has not been established, and some detailed observational studies have found a real risk of late HDN after the oral administration[8;21;22.]

The inferiority of oral vitamin K administration was confirmed in a review of national Dutch, German, Swiss and Australian data23. The only regime comparable in efficacy to the IM administration was an oral daily dose of 25 g until 13 weeks of age, which implies serious practical problems, particularly those generated by compliance to the recommendation.

Practical Recommendation:

Since fat-soluble vitamin reserves are constituted during the last stage of pregnancy, supplementation until the kangaroo baby reaches full term is reasonable.

Recommended doses are as follows:
Vitamin A: 2000-2500 IU/day
Vitamin D: 400-800 IU/day
Vitamin E: 25 IU/day

Following the latest debates on vitamin K, the IM route is indicated at birth. In cases of long-term antibiotic treatments or digestive or liver disease supplementary doses, either IM or orally, could be administered. Given that preterm babies in KMM present a liver immaturity at least until they reach full term and their nutrition is mainly based on breastfeeding, the administration of 2 mg orally and weekly until full term seems to be a possibly effective and safe option.

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APPENDIX 7
PRACTICAL ASPECTS OF BREASTFEEDING IN PRETERM INFANTS

There are many good quality resources to aid health care professionals in practical aspects of the initiation and mantainance of breastfeeding for preterm and low birthweight infants, particularly when the initial separation of mother-baby prevents an early, adequate interaction.

For practical purposes, please visit the Fundación Canguro Web page, practical guidelines of the Kangaroo Mother Method.
http://kangaroo.javeriana.edu.co/reglas_kmc.html