McMaster University

Methodology and guidelines for conducting follow-up of KMC Premature infants

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Background for intervention: Preterm

- Premature children are vulnerable to deficits in almost every area of development
- Vulnerability increases if reared in an environment of minimal stimulation
- Lower socioeconomic environment poses a double hazard

Common belief that early stimulation offers an effective means of developmental intervention

Who is at Risk?: Vulnerable Children

0.5 - 3% of children < 3 yrs at risk for cognitive & developmental disabilities. Those at high risk are:

- **Due to biologic damage e.g. genetic or LBW**
- **Young, lower educated mothers**
- **Minority status**
- **Economically and educationally disadvantaged families, poor home environment/ neighbourhoods**
- **Parental neglect or abuse**

The incidence of disabilities is higher in low resource countries

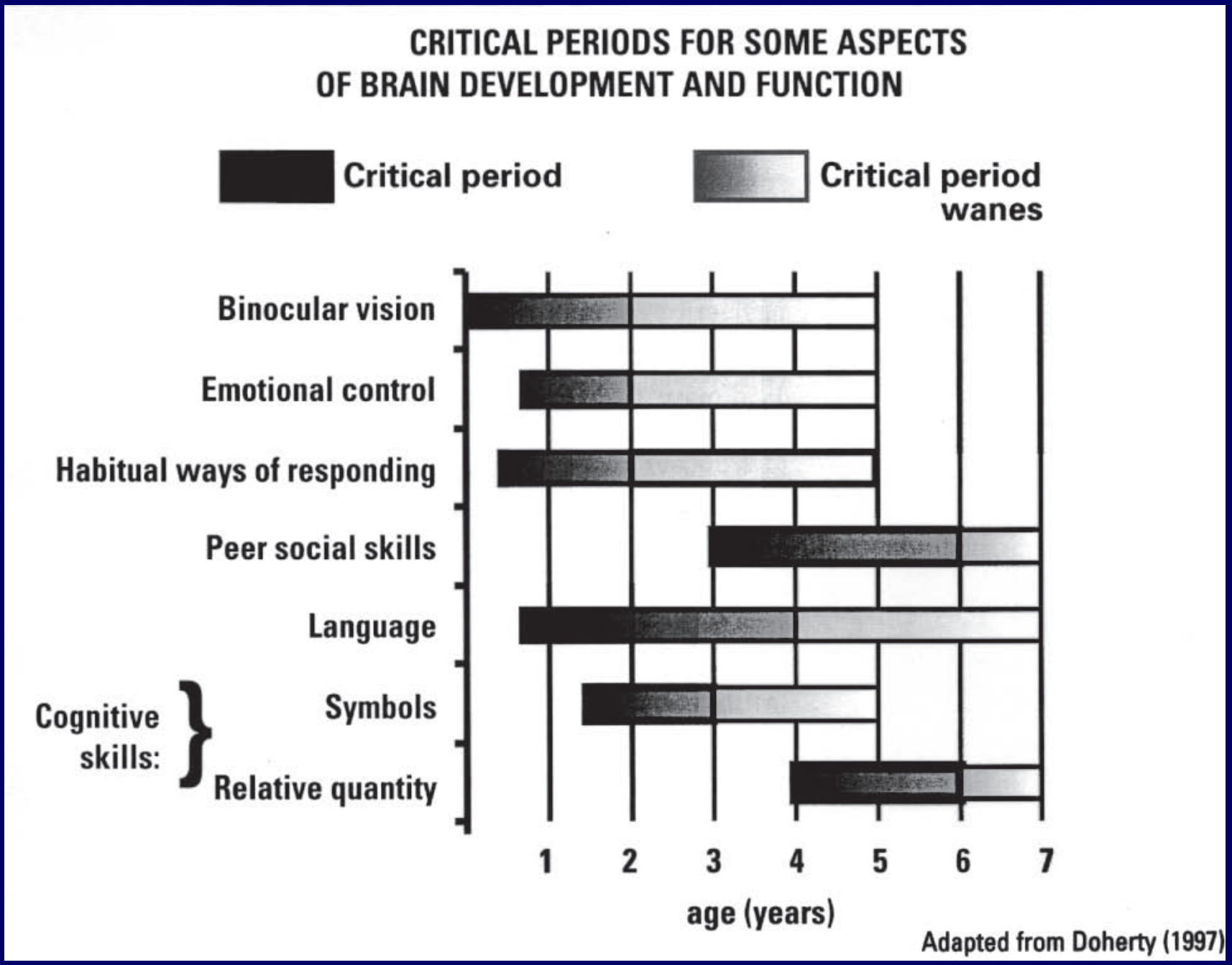
Impact of Poverty in Childhood

- Impact of poverty is above and beyond other sociodemographics (education, occupation, race, single parent)
- Poverty during early childhood (1-5 yrs) was more detrimental than if it occurred later (6-10; 11-15 yrs), in terms of it's association with high school graduation and post-secondary education

Critical and Sensitive Periods

- **Critical period** is a window of opportunity in early life when the child's brain is exquisitively primed to receive sensory input, and develop more advanced neural systems, provided conditions are favourable… these wane by 6 yrs of age.
- **Sensitive period** is a time window during which abnormal conditions can modify the structure or function of a cortical region.

Doherty 1997


CRITICAL PERIODS FOR SOME ASPECTS
OF BRAIN DEVELOPMENT AND FUNCTION
Critical period
Critical period wanes
Binocular vision
Emotional control
Habitual ways of responding
Peer social skills
Language
Cognitive skills:
Symbols
Relative quantity
1
2
3
4
5
6
7
age (years)
Adapted from Doherty (1997)

Human brain development

- Human brain development is relatively slow compared to other primates
- Growth in cortical connections and complexity occurs after 25 wks GA
- Can interventions in the neonatal unit in the critical period of brain development *"override"* the adverse effects of prematurity and neonatal events?

What is Brain Plasticity?

- Plasticity refers to the brain's unique ability to consistently grow, change and remap itself; the brain can also '*repair*' itself, to some extent, by moving the activities to another area so as to allow recovery of function.
- The immature brain of a preterm infant grows and creates neural networks at an unprecendented rate as the brain is flooded with new sensory input.

'Plasticity' of the developing brain

- Brain plasticity is critically dependent on the environment in which the infant is reared
- Dynamic interplay between the child's biology and the child's environment: *Transactional model* proposed by Samaroff and Chandler, 1960's
- Good environmental cues can enhance the flexibility of the brain by 'exercising' it

Intervention Programme: Definition

Early intervention is defined as ***"an organized program of enrichment designed to provide developmentally appropriate activities to babies and toddlers who have been, or who are at risk for a variety of conditions…"***

Denhoff, 1981

Conflicting Assumptions re Interventions in Preterm

- Do premature infants suffer from *deprivation* of the sensory stimuli they were programmed to receive in-utero (Field's massage therapy)?
- Or conversely, are they *overloaded* with sensory information that cannot be programmed properly (Als' NIDCAP theory)?

Feldman & Eidelman , 1998

Who does intervention work for?

Intervention works in selected samples:

- **More mature premature babies >2000g**
- **Little or no effect seen in the smaller, most vulnerable and those with CP, ie. *not often effective for those that need it the most***
- **Positive effects not remarkable in well-conducted studies or in meta-analyses**
- ***Infants from socioeconomically disadvantaged families are likely to benefit most from most interventions, particularly maternal educations***

Why do intervention effects not last longer?

- The decline in scores after intervention has stopped may reflect that the *intensity* or *duration* of intervention may be inadequate
- The intervention is not appropriate
- Were the right outcome measures selected?
- Some brain injuries are irreversible
- Need to study functional changes in the brain to better understand how stimulation impacts (*or does not)* specific areas of the brain

Objectives today:

- To discuss the methodology and design of intervention trials in the context of KMC
- Discuss the important issues in conducting trials to minimize biases
- Review criteria for quality of evidence to make evidence-based recommendations

Intervention studies measuring 'soft and subjective' outcomes are the most difficult to conduct and therefore require rigorous methodology for the results to be accepted.

Questions When Designing Intervention Programs for Infants & Toddlers

Questions for Intervention Programs

- Do the programmes work?
- If so, how do they work?
- For whom do they work?
- Does “one size fit all?”

Questions for Intervention Programs …contd

- Who should be enrolled and when?
- What type of therapy, how often, for how long?
- Who should provide therapy?
- Should it be home-based / centre-based or both?
- Are there any potential hazards?

KANGAROO CARE

Questions re Intervention with KMC

Questions that should be asked before considering KMC:

- **Is the efficacy of intervention with KMC appropriate to be determined through an RCT? -** ***Yes***
- **Is it ethical, feasible and cost-effective?** ***Yes, Yes, and ?***
- **Is the intervention one that can be implemented outside the trial context and possible to apply?** ***Yes***

Infant Health and Development Program

An example of an intervention that is difficult to implement outside the trial, despite good design and stratification across USA

- **Multi-model intervention, including parent education/ parental participation/ monthly meetings, and transport of infants to day care, age 12-36 months.**
- **Unclear which individual component is effective**
- **Good design and stratification across USA**
- **Extremely expensive (>$14,000 per child/ yr)**

JAMA 1990;263:3035-42

KMC: RCT in India

206 infants <2000g BW randomized to KMC and standard care

KMC group had higher:

- **Wt gain/ d (24g vs 16 g, p<.0001)**
- **Weekly HC (0.75cm vs 0.49 cm, p<.02)**
- **Weekly length (1.0 cm vs 0.7 cm, p<.008)**
- **Better control of temperature, hypoglycemia and**
- **sepsis**
- **No impact on duration of hospitalization**

Longer term follow-up not done (?)

Suman R, Udani R, Nanavati R. Ind. Pediatr 2008;45:17-23

KMC for growth of VLBW infants at term

N = 140 VLBW, RCT, *stable infants*

- **At term, no differences in average wt gain, breast feeding rates, sepsis, apnea, hypoglycemia and duration of hospitalization**
- **11.5 days of intermediate care were saved**
- **KMC is an effective as conventional care in NICU without an increase in morbidity and mortality in *stable* VLBW "infants"**

(?) No studies on follow-up of KMC in India

Ghavane et al, Acta Paeditr 2012

METHODOLOGY
and
STUDY DESIGN

Intervention studies: Methodological issues

- A priori hypothesis determination
- Prospective design , precalculation of sample size
- Population-based or representative sample
- Criteria for the intervention strictly defined
- Objective outcome criteria, primary and secondary
- Blinding of outcome assessors
- RCT; contemporaneous controls
- Compliance, low attrition rates
- Cost effectiveness of intervention

Levels of evidence

I Evidence from randomized controlled trial (s)

II Evidence from controlled trial (s) *without* randomization

III Evidence from cohort or case control analytic study

IV Evidence from comparisons between times or places with or without the intervention

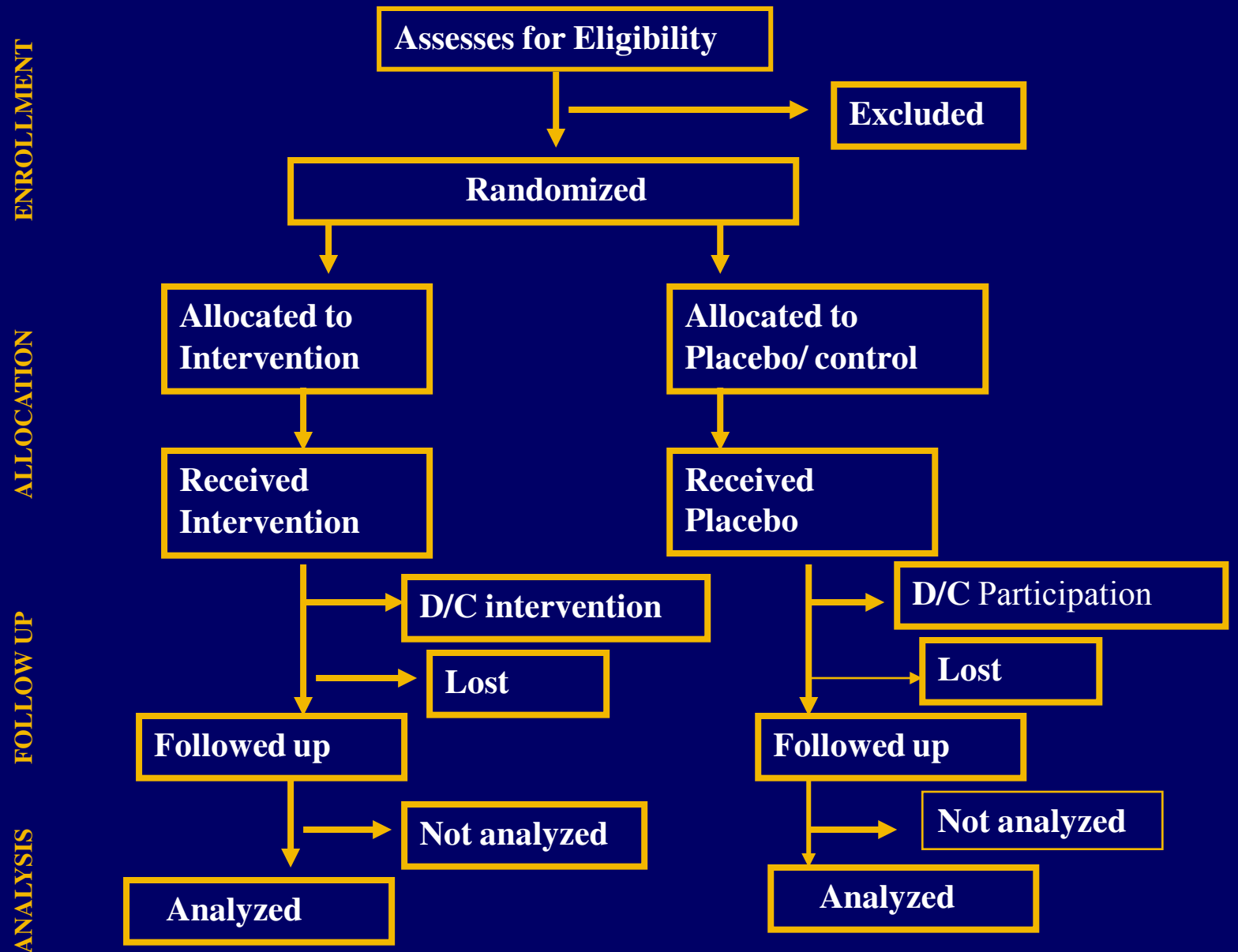
V Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Why randomization?

The advantages of RCTs include:

- It eliminates bias in treatment assignment, specifically selection bias and confounders
- It facilitates blinding (masking) of the identity of treatments from (investigators, participants) outcome assessors in KMC
- It allows a *causal* inference at the end of the trial

4 PHASES of RCT



Stratification of the randomization

- Treatment assignment on the basis of factors known to be strongly associated with the outcome measure e.g. stratification by GA
- Stratification *(limited to 1-2 factors to avoid over-stratification)* will improve statistical efficiency and power, and the trial results will be more convincing

Conduct of Study

Pre-calculation of sample size

- Should be based on the smallest '*effect size*' of benefit that is considered of clinical relevance by parents and health professionals
- Sample size should be plausible depending on the eligible population, and recruitment should be completed within a reasonable time frame
- Significance testing and power requirements should be specified

Piloting of methods and procedures

- Methods should be piloted to ensure study is feasible and outcome measures are reliable
- Check reproducibility, inter-observer variations
- Estimate duration of assessments, response burden

Masking (blinding)

- Every effort should be made to mask investigators, staff and parents to reduce the possibility of bias
- When it is not possible to mask e.g. KMC, cooling for HIE, it is imperative that the staff measuring outcomes are blind to the treatment allocation
- Parents should be advised not to volunteer information on group assignment to the assessors

Measuring outcomes

Selection of outcomes

- Outcomes to be measured should be specified and clearly-defined before the start of the study
- The outcomes selected should be relevant to the child and family, and likely to improve our understanding of the etiology and treatment of the condition

NICU end points in intervention studies

- Lower O_2 requirements/ better temperature control
- Less apnea and days of ventilation
- Increased rates of breast-feeding
- Better weight gain and in tube-feeding days
- Lower infection rates
- Shorter hospitalization days (PMA at discharge)
- Improved neurobehavioural status
- Improved socialization and higher developmental scores
- Maternal satisfaction
- Cost-effectiveness in the long-term

Outcome measures for longer term follow-up

Requirements: Low-cost and reliable measures for large cohorts

- **Parent questionnaires: mailed / interviews**
- **Screening inventories**
- **Direct assessments: physical / psychometric testing: most expensive**

Choice of tests is based on feasibility, time and finances.

Screening tool: Example
Ages & Stages Questionnaire

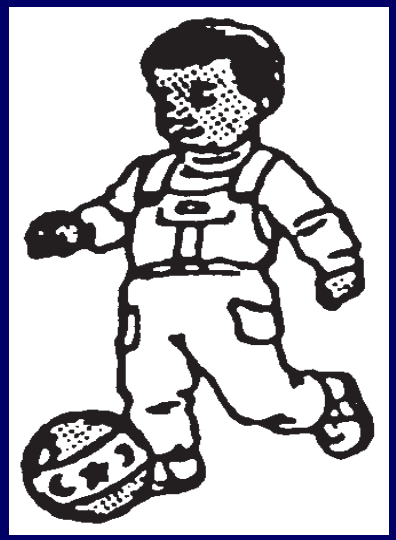
At age 2 years, 6 questions from each domain:

- **Communication**
- **Gross Motor**
- **Fine Motor**
- **Problem-solving**
- **Personal – Social**

ASQ is widely used and is well-validated.

Ages & Stages questionnaire (ASQ)

- Easy pictorial display
- Responses: Yes, sometimes, not yet
- Takes 10 minutes to complete



Example:

Does your child kick a ball by swinging his leg forward?

ASQ: reliability and validity

- Concurrent validity of ASQ and BSID II at age 24 mths in 53 low-risk children: 100% sensitivity and 87% specificity Gollenberg 2010
- ASQ translated into Hindi and administered to the parents (200 children ages 4-24 mths) and compared with DAS II. ASQ has strong characteristics for detecting developmental delay in Indian children Juneja 2012

Standardized assessment tools

- **Screening Tools**
  - Minnesota Child Development Inventory
  - Denver Development Screening Test
  - Ages and stages (ASQ) parent Q
  - BINS (adapted from Bayley)
- **Standardized Developmental Assessment**
  - Bayley Scales of Infant Development- III
  - McCarthy Scales of Children's Abilities
  - Stanford-Binet Test, WIPPSI/ WISC- IV

Standardized assessment tools

- **Language**
  - Peabody Picture Vocabulary Text
  - Mullen Scales of Early-Learning
- **Functional Assessment**
  - WeeFim
  - Vineland Adaptive Behavioural Scales
  - Gross Motor Function (GMFCS)
- **Behaviour**
  - CBCL, BRS

Predictive validity of early cognitive outcomes

- Attainment of subnormal MDI score (<70) on BSID-II is a poor predictor of subsequent subnormal IQ scores at school age in both term and preterm infants. Aylward '05
- 80% of ELBW infants with scores <70 at 20 months had scores above this range at 8 yrs. Early assessments are imprecise and should be used with caution for predictive validity Hack ' 05
- Information on predictive validity of Bayley III is forthcoming

Psychometric testing advantages & disadvantages

Advantages:

- Objective assessments provide a numeric score
- Several domains can be tested by different tests

Disadvantages:

- Expensive and time consuming to administer
- Underestimates IQ of children with disabilities
- Cannot be administered to severely impaired children
- Several different tests required from infancy to maturity
- Predictive validity questionable

Culture test specificity bias

- Tests of intelligence are inevitably influenced by the prior experience and exposure of subjects.
- Test results should not be applied to populations whose cultures are different from the one on which they were standardized.
- Country-specific norms should be established

Role of controls

Controls should be contemperaneous

Advantages :

- **To place the findings of premature cohort in perspective.**
- **To maintain blindness and uniformity in administration of psychometric tests.**

Disadvantages:

- **Expensive and time-consuming.**

Minimum age for reliable assessment

- Neurdevelopmental / neurobehavioural examination at term is a weak predictor of long-term outcome of VLBW infants
- Diagnosis of cerebral palsy can be made reliably at 18-24 months; minor motor problems may not be detected
- Behavioural / emotional problems manifest later
- Subtle cognitive problems / executive functioning may not emerge until more complex array of demands are placed in mid-childhood

Optimal age of assessment early vs late

Early: < 2 years

- Minor neurological findings may be missed
- Too early for cognition and behavioural assessments

Late: > 3 years

- Increase in attrition rate.
- Identify broader morbidity and complexity
- Environmental factors play a greater role than biological factors
- Findings not relevant to the current practice of neonatal intensive care.

Attrition rates

High ascertainment rates are extremely important. With high losses, biases can occur in either direction

- **Children not seen in first attempt, had a 7-fold increased risk of impairments (UK Study)**
- **Children who do not show up were normal**

Untestable subjects: marker variable

Untestable children relative to testable children scored significantly lower on a wide spectrum of abilities at all ages (based on objective tests, semi-structured interviews etc)

Trial monitoring

- Ensure protocol is being implemented correctly
- Document serious side effects
- Pre-planned interim analysis by an external body to check for evidence of very large treatment effects, either positive or negative

ANALYSES

Data collection: collecting the right data

- Experienced person to design data entry forms
- Carefully select variables such as baseline and outcomes
- Including common data sets from other similar trials will allow for pooling of data and meta-analyses

Analyses

- Data should be analyzed on primary collection: i.e. *intention to treat*
- Careful review of infant characteristics that might favour one group should be done
- Adjustments should be made for multiple testing (*doing so will reduce the number of significant outcomes*)

Handling of non-compliant / withdrawn subjects

- Record details of subjects who withdrew or failed to comply and the reasons, to assess potential bias
- Secondary pre-planned exploratory analyses including only compliant subjects is possible, if pre-planned

Meta-analyses

Many studies have small sample sizes and insufficient power to determine the outcomes.

Meta-analysis **is a statistical technique that combines the results of several single studies, calculates the treatment or outcome effect in each study, and then calculates the overall effect of the combined studies.**

Cochrane Collaboration Reviews

The Cochrane Collaboration is an international group of researchers that prepare, maintain and disseminate systematic reviews using a standardized procedure and make clinical recommendations based on the syntheses of the combined studies in the review

Recommendations and Conclusions

KMC has been endorsed by WHO

What are the latest conclusions on KMC?

Is it beneficial?

Current recommendations for KMC

- **Systematic Review:** sufficient evidence to recommend the routine use of KMC for all babies <2000g as soon as they are stable. Up to 500,000 neonatal deaths due to preterm birth complications could be prevented each year in low resource countries if this intervention were implemented at scale Lawn JE, Int J of Epid. 2010:39;1144-54

- **Cochrane Review:** demonstrated benefits in many aspects of the studied outcomes and supports the use of KMC in LBW infants as an alternative to conventional NIC in low-resource settings Conde-Agudelo, 2011

Do we still have 'Equipoise'?

Equipoise is a state in which there is genuine uncertainty about which arm of a clinical trial would be therapeutically superior for the infant. Medical ethics deem it inappropriate to do an RCT if there is known benefit of one treatment over the other.

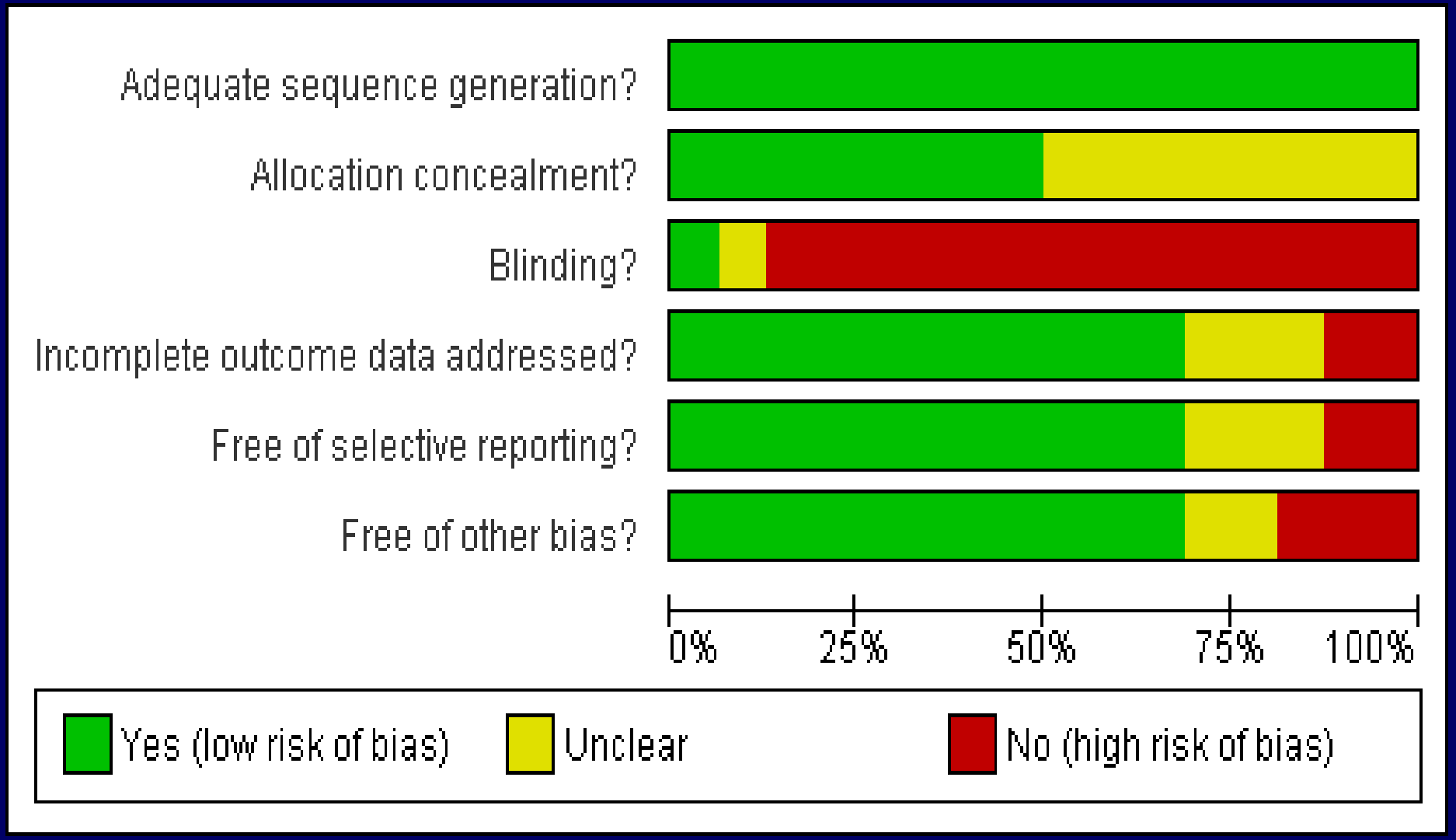
Have we lost our equipoise now?

Kangaroo Mother Care

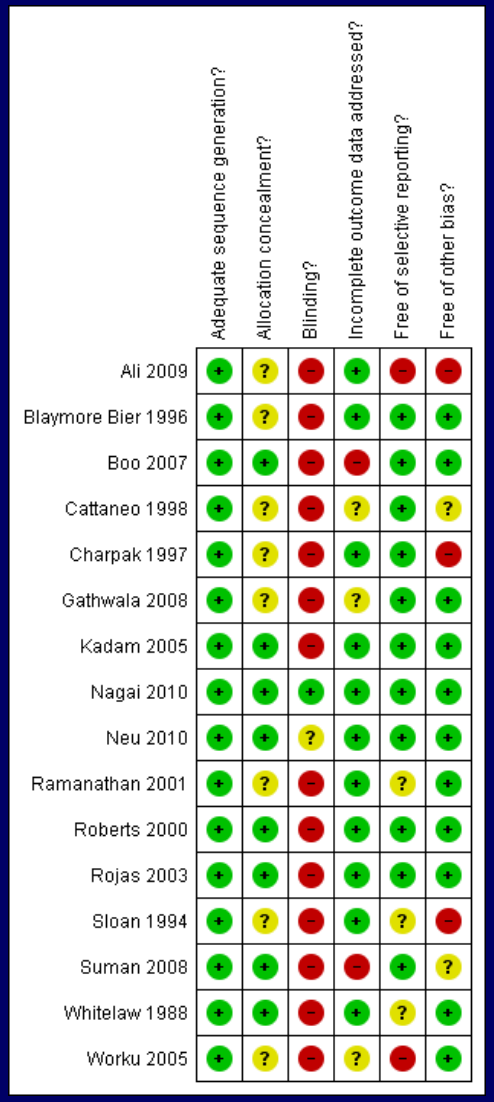
It is an emotionally appealing, low cost intervention that can be implemented in low resource countries as an alternative to conventional neonatal care as well as for periodic bonding opportunity for high-tech NICUs

So what is the problem of using KMC routinely without further trials?

Risk of bias graph: review authors' judgements about each risk of bias item presented as a percentage across all included studies



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Need for methodologically rigorous trials: Cochrane Review

Studies should provide detailed information on :

- inclusion and exclusion criteria
- methods used to generate and conceal the allocated sequence
- measures used to blind outcome assessors to allocation of participants
- completeness of outcome data for all pre-specified outcomes in the protocol
- definition of infant stabilization
- to report adequately infant age at initiation of KMC, frequency, daily duration and total duration of the intervention

Conde-Agudelo, Cochrane Review 2011

Implications for research based on Cochrane Review

- Further explore the effectiveness of early onset continuous KMC in unstabilized or relatively stabilized LBW infants in low-income settings; early vs late KMC
- There is little information on longer-term neurodevelopmental outcomes; continuing follow-up of RCT children are justified as subtle differences in later childhood may become apparent Roberts R 2012

Conde-Agudelo, Cochrane Review 2011

THANK YOU!