InsPECT

a new reporting guideline for the selection and measurement of outcomes in clinical trials

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on behalf of *the InsPECT collaborative research group*

Enhancing Research Impact in Child Health - Child Health Evaluation Sciences CHES

The Hospital for Sick Children, University of Toronto, Canada

SickKids®

Review

nature publishing group

Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies

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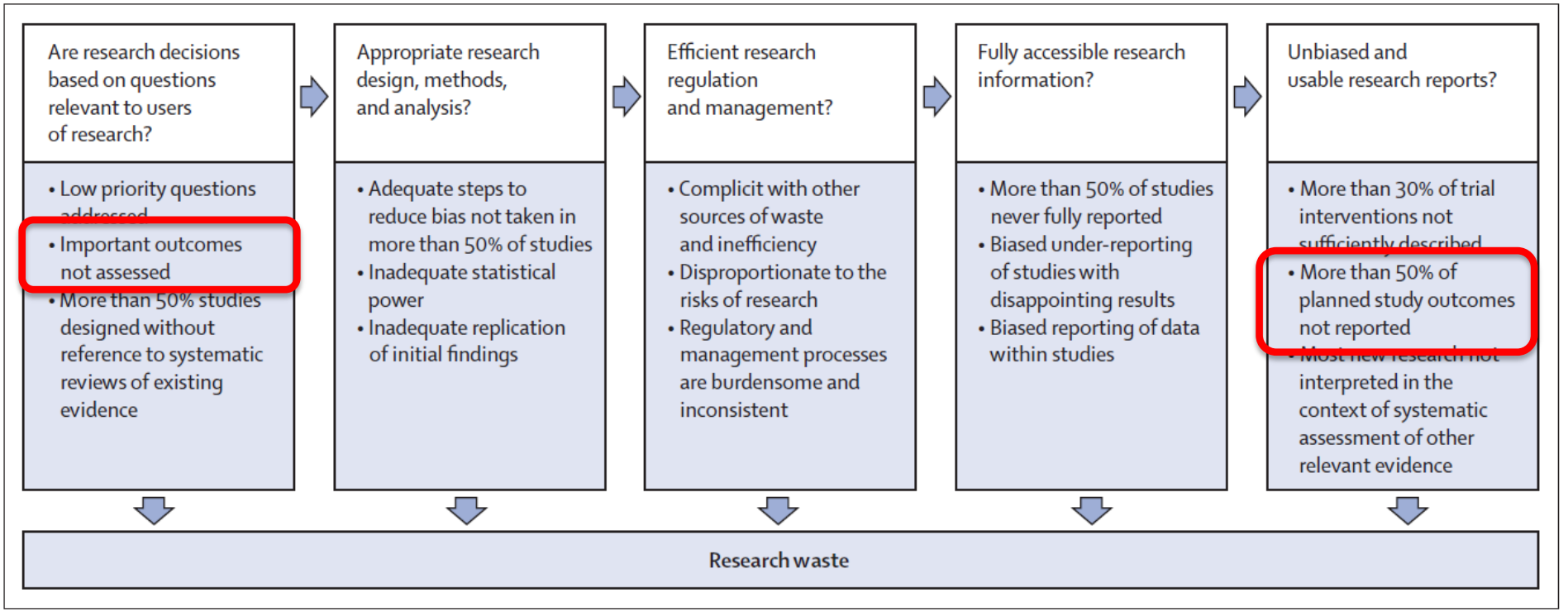
The ultimate goal of neonatal nutrition care is optimal growth, neurodevelopment, and long-term health for preterm babies. Intern
intake
velopment, but after more than 100 y of research the optimum intakes of energy and protein remain unknown. We suggest an important factor contributing to the lack of progress is the lack of a standardized approach to reporting nutritional intake data and growth in the neonatal literature. We reviewed randomized controlled trials and observational studies documented in MEDLINE and the Web of Science from 2008 to 2015 that compared approximately 3 vs. 4 g.kg^{-1}.d^{-1} protein for preterm babies in the first month after birth. Consistency might be expected in the calculation of nutritional intake and assessment of growth outcomes in this relatively narrow scope of neonatal nutrition research. Twenty-two studies were reviewed. There was substantial variation in methods used to estimate and calculate nutritional intakes and in the approaches used in reporting these intakes and measures of infant growth. Such variability makes comparisons amongst studies difficult and meta-analysis unreliable. We propose the StRONNG Checklist—*St*andardized *R*eporting *O*f *N*eonatal *N*utrition and *G*rowth to address these issues.

questions are the optimal protein and energy intakes and the growth velocity that is predictive of optimal long-term health
at the target for growth of the
ch intrauterine growth of the normal human fetus. To achieve this, we need to know, first, what this growth looks like in terms of not only weight but also other measures of growth, including body composition, and, secondly, the nutritional requirements needed for this growth to be realized. This review will consider these critical questions and will propose that a standardized approach to reporting data will aid progress toward answering these unresolved questions.

The many different approaches taken to reporting nutritional intake data and growth in the neonatal literature make addressing these questions through interpretation of the data difficult. To investigate the variability in reporting, we identified and reviewed recent randomized controlled trials and observational studies documented in MEDLINE and the Web of Science from 2008 to 2015 that compared approximately 3 vs. 4 g.kg^{-1}.d^{-1} protein for preterm babies in the first month after birth. Consistency might be expected in the calculation of nutritional intake and assessment of growth outcomes in this relatively narrow scope of research. Twenty-two studies were reviewed. Many of the studies did

‘Research waste’ – Lancet 2014



- “$220 billion wasted on inadequate production and reporting of biomedical research. (…)
- Goes from problems formulating research questions we are asking all the way to papers being published. (…)
- Impact on patients, research teams and impedes improvements in clinical care.”

PLOS | MEDICINE

ESSAY

Why Most Clinical Research Is Not Useful

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Summary Points

- Blue-sky research cannot be easily judged on the basis of practical impact, but clinical research is different and should be useful. It should make a difference for health and disease outcomes or should be undertaken with that as a realistic prospect.
- Many of the features that make clinical research useful can be identified, including those relating to problem base, context placement, information gain, pragmatism, patient centeredness, value for money, feasibility, and transparency.
- Many studies, even in the major general medical journals, do not satisfy these features, and very few studies satisfy most or all of them. Most clinical research therefore fails to be useful not because of its findings but because of its design.
- The forces driving the production and dissemination of nonuseful clinical research are largely identifiable and modifiable.
- Reform is needed. Altering our approach could easily produce more clinical research that is useful, at the same or even at a massively reduced cost.

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Study *Design - Conduct - Reporting*

Decisions needed on

1. **What** to measure
   - Selection of Outcomes <- Core O Sets
2. **How to measure** the outcome
   - Clinimetric Characteristics <- COSMIN
3. How **to report**
   - Reporting standard <- ….

Knowledge gaps

- CONSORT item #6: *"completely define pre-specified outcome measures, including how and when they were assessed"*

What does "completely define" look like?

Sufficient information to: fully describe an outcome; reproduce its measurement in subsequent trials; and combine outcomes in a meta-analysis; its validity; + evaluate the importance to patients and knowledge users; etc.

- SPIRIT item #12: *"Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended"*

Goal

Develop, validate and implement an evidence-informed, consensus-based checklist for outcome reporting in CTs and SRs.

Specific objectives

1. **Development:** Generate evidence underpinning comprehensiveness and relevance of outcome reporting items
   - **Instrument for the reporting Planned Endpoints in Clinical Trials (InsPECT)**
2. **Validation:** Establish the validity, reliability and usability of the InsPECT checklist in multiple disease areas, and obtain global consensus
3. **Implementation:** Generate a comprehensive final checklist and explanatory document that is acceptable, feasible and demonstrates fidelity and sustainability.

Approach

Recommended methodology developing & disseminating reporting guidelines:

1. Literature review of available outcome reporting guidance*
2. Set up a steering committee and methodological/knowledge expert user groups
3. SR to synthesize evidence on the reporting of primary outcomes in CTs and SRs
4. Validation
   - Consensus process (Delphi): to prioritize items, ensure items meaningful to Knowledge Users (patients, clinicians, funders and journal editors)
   - Content validation, feasibility and reliability testing of the checklist with clinical trialists (expertise across ages, disease areas, interventions, outcomes)
5. Implementation
   - Integrated KT plan: Published protocol and SR; Monthly specialty group / annual face to face meetings with International Partners
   - End of grant KT plan: publication of the InsPECT checklist + explanation and elaboration guide (examples of good reporting for each item); dissemination via webinars; partners' social media (Twitter, Facebook); Café Scientifique; conference presentations; open access publication on Equator-Network, "COMET 8-10"

1. Development

What frameworks, guidelines or tools are currently available for reporting of outcomes in drug trials?

Sensitive search

- 16 guidelines on outcome selection
- Generic including the ones from regulators; such as FDA, EMA
- **No guideline on how to report outcomes**

Preliminary **InsPECT tool** developed based on available guidance for reporting outcomes

Offringa et al. submitted

InsPECT (Instrument for reporting Planned Endpoints in Clinical Trials) - Preliminary Checklist

Determination of	Item No.	Item (sources reference(s))
What: Description of this outcome	1	Specify the *core area* of the outcome (1) (Use OMERACT Filter 2.0)
	2	Classify outcome as *primary or secondary*, with justification. (2, 9-13)
Why: Rationale for selecting this outcome	3	Justify *qualification* for the health condition in the age group indicated. (1, 6-8)
	4	Provide a well-specified *explanatory model* or evidence from pre-clinical studies showing how the intervention links to the outcome in the pre-specified age group. (1-3)
	5	Explain how this outcome *matches the objective* of the study. (3-5)
How: This outcome is measured	6	Describe the *instrument used to measure* the outcome in the age group, disease and setting of interest; address instrument validity and reliability. (1, 9, 13, 14) (Use COSMIN checklist)
	7	Specify and justify the *responsiveness* of outcome measure to meaningful change (e.g., minimally important difference) in the population of interest. (1) (Use COSMIN checklist)
	8	Describe *feasibility and acceptability* of measuring outcome in population of interest. (15)
Who: Source of information of this outcome	9	Describe *who* assesses the outcome (e.g., health professional, teacher, caregiver).
	10	Describe *training methods and materials* required for outcome assessors to implement outcome instrument and handling/storage of data. (1)
	11	Describe *availability of outcome assessor(s)* when the measurements are required. For multiple measurements specify which assessor are available at different time points. (1)
Where: Measurement location	12	Justify suitability of outcome *measurement location* and availability of all necessary facilities for the time period of intervention in the specified population. (14, 16)
When: Measurement timings	13	Justify the *choice of time point(s)* of outcome measurement.

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Disease Areas

Validation of the checklist: iterative process

- Four disease areas representative of common areas requiring health provider care in diverse age categories representing medical, surgical, acute and chronic conditions
  1. Neonatal respiratory distress syndrome
  2. Pediatric appendicitis
  3. Adolescent and adult anxiety and depression
  4. Hip Fracture in the elderly

HIP ATTACK
HIP fracture Accelerated surgical care and TreaTment trACK

2. Validation

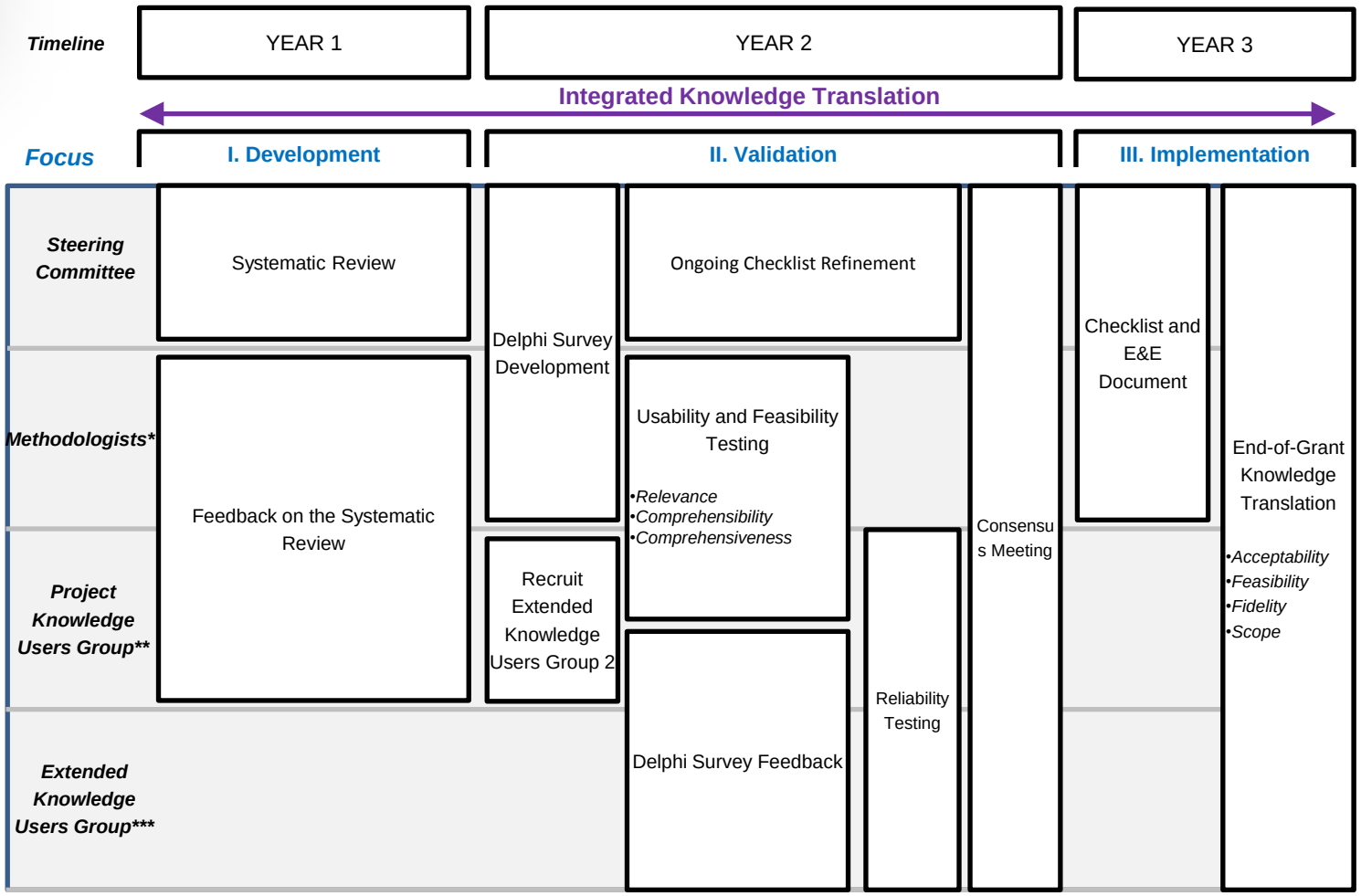
Relevance

- Comprehensibility
- Comprehensiveness
- Usability and user satisfaction (feasibility)

Reliability

- Random sample of 25 SRs and 25 CT's; methods and KU experts apply **InsPECT** independently
  - inter-rater agreement using raw agreement percentages and Cohen's Kappa
  - inter-rater reliability using the ICC

Figure 1. Project Activities, Partners and Knowledge Users involvement, Timelines



*Includes our **partners** *(See our letter of partnership)*: COMET (Core Outcome Measures in Effectiveness Trials), COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments), EQUATOR (Enhancing the QUAlity and Transparency Of health Research), GRADE (Grading of Recommendations Assessment, Development and Evaluation), OMERACT (Outcome Measures in Rheumatology), and **collaborators**; CONSORT (Consolidated Standards of Reporting Trials), PORTaL (Primary Outcome Reporting in Trials), SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), and TIDieR (Template for Intervention Description and Replication).

Includes our **partner: OCHSU (Ontario Child Health Support Unit) and our trialists in the four disease areas.

***Includes journal editors, regulators (deciding on market authorizations), guideline developers, HTA (health technology assessment) practitioners, clinical trial registries, funding agencies, health care providers, patients and families.

Impact - *fully reported outcomes* help…

- Increase trial reproducibility
- Interpret and compare results across studies
- Pool data in meta-analyses
  - Estimate intervention effects more precisely
- Inform future trial decisions
  - Sample size calculation
  - DMSC, stopping rules
  - Recruitment into the trial
- Increase “usefulness” trial results for decision making
  - Reduce “waste”

InsPECT Collaborative Research Group

Steering Committee

Methods Experts and Knowledge Users

InsPECT

Instrument for the reporting of Planned Endpoints in Clinical Trials