# PREgnancy Nutrition: a protocol for the development of a Core Outcome Set (PRENCOS)

# Sarah Louise Killeen1, Eileen C O’ Brien1, Chandni Maria Jacob2, 3, 4,Sharleen O’Reilly1, 5, Mark Hanson 2, 3, 4, Fionnuala M McAuliffe1

# 1 UCD Perinatal Research Centre, School of Medicine, University College Dublin, National Maternity Hospital, Dublin 2, Ireland

2 Institute of Developmental Sciences, University of Southampton, Southampton, United Kingdom

3 Academic Unit of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

4 NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

5 University College Dublin, School of Agriculture and Food Science, Science Centre South Belfield Dublin 4

# Review Article

Contact details of author:

Prof. Fionnuala McAuliffe

Fionnuala.mcauliffe@ucd.ie

UCD Perinatal Research Centre, School of Medicine, University College Dublin,

National Maternity Hospital, Dublin 2, Ireland

Key words:Pregnancy, nutrition, core outcome set, outcomes, maternal health, diet

## Synopsis

This study will develop a Core Outcome Set for pregnancy nutrition research, which is relevant to multiple stakeholders internationally.

**List of abbreviations**

COS – Core Outcome Set

COMET - Core Outcome Measures in Effectiveness Trials

COS-STAD STAndards for Development of Core Outcome Sets

CROWN - Core Outcomes in Women and New-born health initiative

DOHaD – Developmental Origins of Health and Disease

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

# Word count of main text: 3661

# Abstract (195 words)

## Background

Nutrition during pregnancy is a modifiable risk factor for maternal and child outcomes and an important consideration in pregnancy management. No core outcome set (COS) exists for nutrition during pregnancy and current high levels of variability limit study comparability, which is a barrier to high quality evidence generation that can inform practice.

**Objective**

To develop a COS for pregnancy nutrition research that is relevant to varied stakeholders and resource settings.

## Methods

We will conduct a systematic review of studies evaluating nutrition during pregnancy and extract all outcomes identified. We will supplement these outcomes with those identified through qualitative interviews with mothers. We will then invite healthcare professionals, researchers and mothers from various international resource settings to participate in a two-round modified Delphi survey. The survey will identify the most important outcomes to include in the COS. Finally, we will hold a consensus meeting with a select group of participants to finalise the COS.

## Conclusion

This COS will support standardisation of outcomes in pregnancy nutrition research and ensure that selected outcomes are considered important by a variety of stakeholders. This will enhance the evidence behind nutrition interventions in pregnancy to improve outcomes for pregnant women.

## Introduction

Maternal nutrition and diet influences the intrauterine environment of the developing fetus. This has the potential to impact maternal health, pregnancy and infant outcomes and through Developmental Origins of Health and Disease (DOHaD), may affect the health and development of her child from childhood through to adulthood1-5. Therefore, maternal nutrition during pregnancy is an important consideration in the management of pregnant women and in the overall life-course approach to healthcare and health promotion. The outcomes reported in individual studies influence decisions made in clinical practice, resource allocation, research priorities and future study design and therefore are of critical importance within scientific research6. While numerous trials evaluating the effect of dietary interventions in pregnancy exist, outcome selection and reporting within these studies is largely inconsistent. A recent systematic review of diet and lifestyle interventions in pregnancy identified 142 different outcomes and over half (51%) of those appeared only once7. This is a barrier to high quality evidence generation as it limits our ability to compare and combine findings from individual studies in systematic reviews or meta-analyses and leads to significant research waste.

A core outcome set (COS) is a set of outcomes identified by consensus to be a minimum reporting standard within an area of research8. Once defined, the expectation is that these outcomes will be consistently reported in all relevant research studies. This does not however restrict the inclusion and reporting of additional outcomes not included in the COS. Recognising the current inconsistency in outcome reporting within maternal and new-born medicine, over 80 editors of women’s health journals formed a consortium and launched the Core Outcomes in Women and New-born health initiative (CROWN) ([www.crown-initiative.org](http://www.crown-initiative.org)). The aim of this initiative is to support the development, dissemination and use of COSs in maternal health research. In addition to facilitating the comparison and amalgamation of results from individual studies, COSs have the potential to reduce reporting bias within scientific research and therefore improve study quality9. At present there is no COS focused specifically on nutrition in pregnancy. Therefore, we aim to develop such a COS for use in studies evaluating nutrition in pregnancy and this protocol provides a detailed overview of the process for developing the COS.

## Methods

This study protocol was prospectively registered in the Core Outcome Measures in Effectiveness Trials (COMET) database (COMET) (http://www.comet-initiative.org/studies/details/1273). The study design follows the COMET handbook (Williamson et al 2017) and COS-STAD (minimum STAndards for Development of Core Outcome Sets) 10 and will involve three distinct phases (Figure 1). The first phase will generate a full list of potential outcomes for inclusion in the COS, which will be carried forward into the next phase. This will be done through a systematic literature review to identify all outcomes reported in pregnancy nutrition research. It is assumed that the opinions of healthcare professionals and researchers are sufficiently captured in the literature review. We will supplement the systematic review findings with qualitative interviews with women to identify any outcomes of importance to these stakeholders. The second phase will involve a modified Delphi survey including a variety of international stakeholders. The aim of this phase is to refine the list of outcomes identified from the first phase into a smaller subset of outcomes for inclusion in the COS. The third and final phase involves a consensus meeting where outcomes that did not reach consensus in the second phase will be discussed and voted on for inclusion in the final COS. Ethical approval has been provided from the National Maternity Hospital and all procedures will be completed in line with the Declaration of Helsinki.

##### Figure 1: Study design overview

## Phase 1: Outcome identification

### Part A: Systematic review

We will perform a systematic review of studies evaluating the effect of maternal nutrition interventions or exposures during pregnancy. The full protocol including the search strategy will be available online via the PROSPERO database and the review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines11.

#### Identification of relevant studies and guidelines

We will search major electronic databases including PubMed, Embase, CINAHL, clinicaltrials.org, and the Cochrane Library for studies on nutrition interventions and exposures in pregnancy. Adaptations to the search strategy will be made for each database and we will include records categorised as “in progress” or E-pub ahead of print. We will also hand-search the reference list of relevant studies to identify any additional publications not identified by our search. Records from each database will be combined and duplicates removed. We will limit our review to studies published in English and since 1990.

#### Identification of eligible studies and guidelines

The primary research question is “What outcomes have been reported in studies involving antenatal nutrition interventions or exposures?” Studies will be eligible for inclusion if they involve an intervention during pregnancy which aims to result in changes in dietary and/or macronutrient intakes (e.g. dietary advice, supplementation or behavioural change) or involve observations between dietary indices (e.g. food intakes, diet quality, macronutrient intake) and outcomes. This can be with pregnant women of any age, any gestation and conducted in any setting. Multicomponent interventions where diet is combined with another lifestyle or physical activity intervention will also be included. We will not include studies that involve single or muti-micronutrient interventions or observations only. Therefore, studies will be eligible for inclusion if they are experimental or quasi-experimental, cohort studies or cross-sectional studies. Systematic reviews and meta-analyses will also be included to identify any potential newly generated composite outcomes. However, individual outcomes identified within the systematic reviews will not be extracted. Case reports, case series, case-control studies, commentaries, letters to the editor, narrative reviews and expert opinions will be excluded.

Titles and abstracts of identified studies will be independently screened by two reviewers. Any discrepancies from this initial assessment will be resolved by involving a third reviewer and if necessary, discussion with the wider research team. Studies will be classified as potentially eligible, ineligible and unclear. The full text of unclear and potentially eligible studies will be obtained and independently assessed for inclusion by two reviewers. Any studies excluded at this stage will have the exclusion reason documented. Records will be managed using Mendeley.

#### Data extraction

Outcomes (including primary, secondary and composite outcomes) from eligible studies will be extracted by two independent reviewers using a standardised data extraction tool. Data on study characteristics will be recorded such as author details, study population, study type, nature of nutrition intervention or exposure, sample size, location of study and date of publication. The definition of each outcome, location of outcome reporting within the paper and the chosen method for outcome measurement will also be collected. As the aim of this review is to identify a long list of outcomes for consideration for inclusion in the Core Outcome Set, we will not assess risk of bias in studies. This is acceptable based on suggested COS development methodology8. Study authors will be contacted in the case of missing or unclear information. The study outcomes will be categorised based on the taxonomy of the COMET initiative11. Any disagreement in categorising the identified outcomes will be resolved by involving a third reviewer. We will combine outcomes that are clinically similar to refine the initial outcome list and simplify the consensus process. This is based on recent evidence that having higher numbers of items within a Delphi consensus survey is associated with significantly lower response rates12.

#### Data analysis

We will report the systematic review results in accordance with PRISMA guidelines11. The characteristics of the study will be narratively described and findings will be presented in texts and tables with the reporting frequency of each outcome. We expect high heterogeneity in the outcomes reported based on previous reviews; hence outcomes will be reported as a list with frequencies.

#### Outcome definitions

Once a preliminary list of outcomes is identified and characterised through the systematic review, we will develop lay definitions for each outcome that will be piloted in our qualitative interviews.

### Part B: Qualitative interviews

This part of the outcome generation phase will determine which outcomes pregnant women and mothers think are important for inclusion in the COS. This is an important step as the opinion of these stakeholders may be under-represented in scientific literature8. A sample size of n = 30 will be considered sufficient to achieve data saturation and to ensure that adequate and quality data are collected to provide a detailed understanding of the priorities and opinions among this group. To ensure a global perspective, we also aim to include pregnant women from LMIC.

#### Participants

We will recruit women through the outpatient department of the National Maternity Hospital in Dublin and purposively recruit women from a broad range of demographics. This recruitment will be supplemented with contact on social media, online pregnancy and parent forums, and with national and international advocacy groups and organisations such as dietetic or medical professional bodies (e.g. Irish Nutrition and Dietetic Institute, International Federation of Gynecology and Obstetrics). Women will be eligible to participate if they have an adequate level of oral English or the availability of an interpreter. The location of each participant interview will be documented and be reported by country. At the time of recruitment, informed consent will be obtained and we will request information such as gestational age (where relevant), parity, co-morbidities and demographics prior to commencing the interviews.

#### Qualitative interview structure

Qualitative interviews will be conducted in person or via telephone. After providing some background to the study, we will ask women to list all of the outcomes they think are important to measure and report in a study examining nutrition in pregnancy. Once the participant has exhausted their spontaneously generated outcomes, we will present our outcome list from the systematic review in the Delphi survey format, along with the suggested lay definitions (this will be read out to participants during telephone interviews). Where feasible, we will also pilot an example of a Delphi survey with the women and through a “think aloud” process, we will ask participants verbally explain their thoughts on all aspects including comprehensibility, usability and clarity. Finally, we will show women an example of our proposed feedback form that we plan to produce between rounds in the Delphi survey. The aim of this is to ensure comprehension by this stakeholder group prior to commencing the Delphi survey8.

#### Data synthesis and analysis

Both in-person and telephone interviews will be digitally recorded and transcribed for qualitative data analysis. At this stage, all data will be anonymized. All transcripts will be analysed by a single researcher and a second researcher will independently analyse 10% of transcripts to ensure agreement. Any differences in coding will be resolved by consensus. Any novel outcomes will be recorded and categorised following the taxonomy used for part A in the systematic review.

#### Refinement of outcome definitions

Interview feedback on the outcome definitions will be analysed. Where necessary and appropriate, the specific language used by the women will be incorporated into the lay explanations to enhance their applicability to Delphi survey participants.

### Phase Two: Delphi survey

We will conduct a modified Delphi survey with representatives from all relevant stakeholder groups internationally. This is an iterative consensus process during which, we will ask participants to rank how important they think outcomes are to include in the final COS. In this survey, we will provide participants with the full list of outcomes refined from phase 1 and ask them to rank each of these outcomes on how important they are to include in the COS. We will provide clear guidance on the distinction between a “key data point” necessary to interpret the effect of an intervention/exposure and an “outcome” which provides an indicator of the intervention/exposure effect.

*Study participants*

We will include the following groups in the survey: pregnant women and mothers; clinicians and other healthcare professionals involved in the care of pregnant women; and researchers with an interest and expertise in studying pregnant women and/or nutrition. Women will be recruited as per Part B’s qualitative interviews and recruitment fora will include pregnancy clinics, parenting forums, advocacy groups and social media. Clinicians will be recruited through members of national and international societies/professional associations. These will include obstetricians, gynaecologists, general practitioners, midwives, public health nurses, nurses, and allied health professionals such as dietitians. All clinicians and relevant healthcare professionals will have significant experience working with pregnant women. Researchers will include those with an interest and experience in pregnancy. They will be recruited through the author lists of included studies in the systematic review as well as use of outreach with international research organisations/networks. As the information about and link to the Delphi survey will be circulated via email, the email addresses of any potential participants will be requested for this purpose. We will invite participants from a variety of backgrounds and include representatives from Canada, the USA, Europe, Africa and the Asia-Pacific. We will aim to have a comprehensive spread of international participants so that we can incorporate the perspectives of individuals from or working in different practice settings with varying resources. Where necessary, we will also ask interested parties to recommend additional colleagues or peers to take part so that we ensure participation is broad, inclusive and comprehensive.We aim to include a minimum of 20 participants within each stakeholder group for the first round of the Delphi survey.

#### Communication with participants

In the initial email invitation, we will include stakeholder-specific information outlining the project background, the Delphi purpose and process, and the potential impact of their participation on nutrition research within this population group6. The email will also include an electronic consent form and brief demographic questionnaire to collect information such as the type of stakeholder they represent, their age, country of residence, sex, and experience with any COS development along with other relevant stakeholder-specific questions (e.g. parity for women and mothers). Participants who express interest in taking part in the survey and return the consent form will be sent a link to the Delphi survey along with detailed instructions. The survey will be disseminated using DelphiManager**™** software (developed by the COMET initiative)13.

#### Delphi survey structure

The Delphi survey consists of two rounds and we will retain all items from the first round in the second. Consensus is not necessary for all outcomes as the purpose of the survey is to define which outcomes are essential for COS inclusion. Any outcomes without consensus after the survey’s second round will be discussed at the consensus meeting. All survey data will anonymized and only the local core study team will have access to the full list of Delphi survey participants.

##### Round one

The first round of the Delphi survey will be close-ended (modified Delphi survey). We will provide participants with the full list of outcomes for consideration and ask them to rank the importance of including each outcome in the final COS using a 9-point Likert scale as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group14. Scores of one–three will be considered “not essential” for inclusion, scores of four–six “important but not critical” for inclusion and scores of seven–nine considered “critically important for inclusion”. Participants will also be given the opportunity to select “unable to score” where appropriate. Beside each outcome, there will be an option to provide free text to justify answers provided but this will not be mandatory. A single open-ended question will be provided at the end of the first round survey which can be used by stakeholders to provide any additional outcomes they think should be considered for inclusion but were not identified through phase one of the study. Any new outcome will be categorised, discussed within the core research team and if appropriate, will be brought forward to round two of the survey.

##### Round two

In the second and final round of the survey, we will provide each participant with their scores for each outcome and the collated scores for each stakeholder group. Based on this, participants will have the opportunity to change their scoring for each outcome or retain their original score. Participants will also be asked to rank any newly identified outcomes and if they would like to participate in the face-to-face consensus meeting.

#### Data analysis and inter-round feedback

We will generate descriptive statistics after each round based on the different stakeholder groups involved in the Delphi survey. We will identify the number of participants scoring each outcome and distribution of scores stratified by stakeholder type. In round two of the survey, we will provide each participant with their round one score for each outcome and the mean or median for each of the stakeholder groups. Participants will be blinded to the other participants and their individual scores.

#### Consensus

Consensus levels will be set *a priori.* “Consensus in” will be defined as at least 70% of each stakeholder group participants score the outcome as “critically important for inclusion” and less than or equal to 15% of participants score it as “not essential”. The level for excluding an outcome from the final COS will be defined as at least 70% of each stakeholder group participants score it as “not essential” and no more than 15% of participants score it as “critically important for inclusion”8. Outcomes that fail to meet either of these conditions will be considered to have reached no consensus and will be brought forward to the consensus meeting.

#### Minimizing attrition

Non-responders will be pre-defined as those who do not complete the Delphi first round despite two email reminders, each of which will be two weeks apart. For those who complete round one of the survey, a response rate of 80% or greater for each stakeholder group will be deemed acceptable12. We will classify drop-outs as those who complete the survey’s first round within the initial 6-week period but fail to complete the second round within the same timeframe despite three reminder emails. Participants who do not complete the first round of the survey will not be invited to the second round. Where possible, we will try to align the timing of the Delphi survey to relevant international meetings, conferences and congresses with the aim of improving response rates and speed of the project15.

### Phase 3: Consensus meeting

The third and final phase of this study is the consensus meeting. We will hold a face-to-face meeting with at least ten participants from the phase two Delphi survey. Participants will be selected from those who indicated their interest within the Delphi Survey. A pragmatic approach will be taken on the numbers attending based on the location and timing of the meeting. Attendees will provide consent via email prior to the meeting.

#### Meeting structure

The meeting will be a guided discussion with the Delphi survey results presented initially and through nominal group technique, stakeholder opinions will be collected and organised. The focus of the meeting will be on the outcomes for which consensus was not reached. All attendees will be reminded of the Delphi survey results, including their individual scores for each outcome and the average score of each stakeholder group, prior to the meeting. Once the results have been reviewed, participants will be asked to vote anonymously for the outcomes that should be included in the final COS. If there are any remaining outliers, we will review these through further discussion applying nominal group technique until consensus is reached.

## Protocol adjustments

Further protocol modifications will occur if logistical considerations mean that changes are required to facilitate the consensus process. For example, participants in the Delphi survey may identify critical issues that need to be amended in subsequent rounds to maximise response rate or we may need to include additional steps to ensure full stakeholder representation6. Any adjustments will be added to the COMET protocol and be described in any future publications.

## Discussion and implementation of the COS

Despite CROWN’s launch, currently still less than 10 published COSs in the area of pregnancy and childbirth exist and the methods used to create them vary16. This study intends to reach international consensus on the most critical outcomes to include in nutrition research in pregnancy from a variety of stakeholders. This will help increase public representation in outcome selection and reduce outcome reporting bias and heterogeneity in relevant research studies. All of which will support high quality evidence synthesis to inform practice and international nutrition guidelines and policies. We selected a modified Delphi survey method as the preferred method to generate consensus due to its anonymity. This will avoid certain biases associated with face-to-face meetings such as the effect of dominant individuals on the opinions of others. In addition, the Delphi survey has the potential to have wide geographical reach that would otherwise not be possible with in-person meetings. This is important to enhance the international relevance of the final COS and ensures the minimum outcomes selected are generally applicable across a variety of research and practice settings and applicable regardless of the variance in resources available and health system structures.

The results of this systematic review will build on the results of Rogozinska’s review in 2017 and may identify additional outcomes through the inclusion of a broader range of eligible study designs and documents. We will publish and disseminate the results of the systematic review and final COS at international obstetrics and nutrition meetings. The dissemination will support the advancement of nutrition research in pregnancy and inform future COS development and implementation of this COS into practice. Archiving of the results will also occur within the COMET and CROWN databases. A COS for pregnancy nutrition will help streamline outcome reporting within nutrition research in pregnancy so that high quality evidence on the most critical outcomes can be generated through systematic reviews and meta-analysis. In addition, identifying key data that should be reported in studies evaluating nutrition in pregnancy will support the enhancement of the quality of literature in this area. This will strengthen the evidence base for nutritional recommendations in pregnancy and aid in the advancement of nutritional care of pregnant women worldwide.

### Author contributions

All authors were involved in the conception and design of the study. SLK wrote the manuscript. SLK, EOB, SOR and FMcA designed the conceptual framework with input from all other authors. All authors provided input into the study design, analytical methods and revisions of the manuscript.

### Acknowledgements

We are grateful to the FIGO Pregnancy Non-Communicable Diseases committee for their support for the protocol

## Conflicts of interest

None

## References

1. Grandy M, Snowden JM, Boone-Heinonen J, Purnell JQ, Thornburg KL, Marshall NE. Poorer maternal diet quality and increased birth weight. J Matern Fetal Neonatal Med. 2018 Jun;31(12):1613-1619.
2. Geraghty AA, O'Brien EC, Alberdi G, Horan MK, Donnelly J, Larkin E et al. Maternal protein intake during pregnancy is associated with child growth up to 5 years of age, but not through insulin-like growth factor-1: findings from the ROLO study. Br J Nutr. 2018 Dec;120(11):1252-1261.
3. Mandy M, Nyirenda M. Developmental Origins of Health and Disease: the relevance to developing nations. Int Health. 2018 Mar 1;10(2):66-70.
4. Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. Clin Obstet Gynecol. 2013 Sep;56(3):511-9
5. O'Brien EC, Geraghty AA, O'Sullivan EJ, Riordan JA, Horan MK, Larkin E, et al. Five-year follow up of a low glycaemic index dietary randomised controlled trial in pregnancy-no long-term maternal effects of a dietary intervention. BJOG. 2018 Oct 10.
6. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. *Trials*. 2017 Jun 20;18(Suppl 3):280.
7. Rogozińska E, Marlin N, Yang F, Dodd JM, Guelfi K, Teede H, et al. Variations in reporting of outcomes in randomized trials on diet and physical activity in pregnancy: A systematic review. *J Obstet Gynaecol Res*. 2017 Jul;43(7):1101-1110.
8. Williamson PR, Altman DG, Blazeby JM Clarke M, Devane D, Gargon E. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012; 13: 132.
9. Kirkham JJ, Altman DG, Chan AW, Gamble C, Dwan KM, Williamson PR. Outcome reporting bias in trials: a methodological approach for assessment and adjustment in systematic reviews. *BMJ*. 2018 Sep 28;362:k3802. doi: 10.1136/bmj.k3802.
10. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. *PLoS Med*. 2017 Nov 16;14(11):e1002447.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009 Oct;62(10):1006-12
12. Gargon E, Crew R, Burnside G, Williamson PR. Higher number of items associated with significantly lower response rates in COS Delphi surveys. J *Clin Epidemiol*. 2019 Apr;108:110-120. doi: 10.1016/j.jclinepi.2018.12.010. Epub 2018 Dec 15.
13. COMET Initiative Delphi Manager 2017. [ONLINE]. Available at: http://www.comet-initiative.org/delphimanager/ [Accessed 27 June 2019]
14. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes*. J Clin Epidemiol*. 2011 Apr;64(4):395-400.
15. Gorst SL, Gargon E, Clarke M, Smith V, Williamson PR et al. Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps. *PLoS One*. 2016 Dec 14;11(12):e0168403.
16. Gargon E, Gorst SL, Harman NL, Smith V, Matvienko-Sikar K, Williamson PR. Choosing important health outcomes for comparative effectiveness research: 4th annual update to a systematic review of core outcome sets for research. PLoS One. 2018 Dec 28;13(12):e0209869.

# Figure legend

##### Figure 1: Study design overview