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Research Article
Maternal medicine

A core outcome set for the treatment of pregnant women with pregestational diabetes: an international consensus study

O Kgosidialwa,[a] D Bogdanet,[a] AM Egan,[b] PM O'Shea,[a] C Newman,[a] TP Griffin,[a] C McDonagh,[a] C O'Shea,[a] L Carmody,[a] SD Cooray,[c,d] E Anastasiou,[e] E Wender-Ozegowska,[f] C Clarson,[g,h] A Spadola,[i] F Alvarado,[i] E Noctor,[j] E Dempsey,[k] A Napoli,[l] C Crowther,[m] S Galjaard,[n] MR Loeken,[o,p] MJA Maresh,[q] P Gillespie,[r] H deValk,[s] A Agostini,[t] L Biesty,[u] D Devane,[u,v] F Dunne,[a] For the INSPIRED Research Group

[a] College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland [b] Division of Endocrinology, Mayo Clinic, Rochester, MN, USA [c] Diabetes and Endocrinology Units, Monash Health, Clayton, Vic., Australia [d] Monash Centre for Health Research and Implementation, Monash University, Clayton, Vic., Australia [e] Department Diabetes & Pregnancy Outpatients, Mitera Hospital, Athens, Greece [f] Department of Reproduction, Poznan University of Medical Sciences, Poznan, Poland [g] Department of Paediatrics, University of Western Ontario, London, ON, Canada [h] Lawson Health Research Institute, London, ON, Canada [i] Mother Infant Research Institute, Tufts Medical Center, Boston, MA, USA [j] Division of Endocrinology, University Hospital Limerick, Limerick, Ireland [k] INFANT Centre and Department of Paediatrics & Child Health, University College Cork, Cork, Ireland [l] Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza, University of Rome, Rome, Italy [m] Liggins Institute, The University of Auckland, Auckland, New Zealand [n] Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands [o] Section of Islet Cell and Regenerative Biology, Joslin Diabetes Center, Boston, MA, USA [p] Department of Medicine, Harvard Medical School, Boston, MA, USA [q] Department of Obstetrics, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK [r] Health Economics and Policy Analysis Centre (HEPAC), National University of Ireland, Galway, Ireland [s] Department of Internal Medicine, University Medical Centre Utrecht, Utrecht, The Netherlands [t] A.S.LViterbo Distretto A, Consultorio Montefiascone, Rome, Italy [u] School of Nursing & Midwifery, National University of Ireland Galway, Galway, Ireland [v] HRB-Trials Methodology Research Network, National University of Ireland Galway, Galway, Ireland

Correspondence: Dr O Kgosidialwa, Galway Diabetes Research Centre, Diabetes Day Centre, Galway University Hospital, Galway, H91 YR71, Ireland. Email: oratile.kgosidialwa2@hse.ie

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Objective To develop a core outcome set (COS) for randomised controlled trials (RCTs) evaluating the effectiveness of interventions for the treatment of pregnant women with pregestational diabetes mellitus (PGDM).

Design A consensus developmental study.

Setting International.

Population Two hundred and five stakeholders completed the first round.

Methods The study consisted of three components. (1) A systematic review of the literature to produce a list of outcomes reported in RCTs assessing the effectiveness of interventions for the treatment of pregnant women with PGDM. (2) A three-round, online eDelphi survey to prioritise these outcomes by international stakeholders (including healthcare professionals, researchers and women with PGDM). (3) A consensus meeting where stakeholders from each group decided on the final COS.

Main outcome measures All outcomes were extracted from the literature.

Results We extracted 131 unique outcomes from 67 records meeting the full inclusion criteria. Of the 205 stakeholders who completed the first round, 174/205 (85%) and 165/174 (95%) completed rounds 2 and 3, respectively. Participants at the subsequent consensus meeting chose 19 outcomes for inclusion into the COS: trimester-specific haemoglobin A1c, maternal weight gain during pregnancy, severe maternal hypoglycaemia, diabetic ketoacidosis, miscarriage, pregnancy-induced hypertension, pre-eclampsia, maternal death, birthweight, large for gestational age, small for gestational age, gestational age at birth, preterm birth, mode of birth, shoulder dystocia, neonatal hypoglycaemia, congenital malformations, stillbirth and neonatal death.

Conclusions This COS will enable better comparison between RCTs to produce robust evidence synthesis, improve trial reporting and optimise research efficiency in studies assessing treatment of pregnant women with PGDM.

Keywords Core outcome set, interventions, pregestational diabetes, randomised controlled trials, treatment.

Tweetable abstract 165 key stakeholders have developed #Treatment #CoreOutcomes in pregnant women with #diabetes existing before pregnancy.

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Introduction

Pregestational diabetes mellitus (PGDM) is defined as diabetes existing before pregnancy (including type 1 and type 2 diabetes mellitus). PGDM affects 1–4% of pregnancies depending on the population.[1,2] PGDM prevalence continues to rise globally,[3–5] partly due to the obesity epidemic and increasing maternal age.[4] PGDM is associated with adverse pregnancy outcomes including congenital malformations,[6] macrosomia,[2] preterm birth[2,7] and increased rates of caesarean delivery.[2,7] It is also associated with worsening diabetes complications such as diabetic retinopathy and nephropathy,[8–10] at least during pregnancy, and developing co-morbidities such as pre-eclampsia and other hypertensive disorders.[11,12] Hence, PGDM poses a significant healthcare and economic burden. As a result, there have been advancements in education,[13,14] technology[15,16] and pharmacology[17] to improve maternal and infant outcomes in women with PGDM.

There is evidence that these advances have improved clinical outcomes for women with diabetes in pregnancy.[18] However, there is no standardised approach to choosing which outcomes are measured or reported, making it difficult to compare and contrast the effects of various interventions and robustly synthesise evidence from a combination of trials.[19] To help standardise reporting of outcomes in maternal diabetes, the International Association of Diabetes in Pregnancy Study Groups compiled and created a repository of definitions for maternal and fetal outcomes to be used universally.[19] This work provides details on 'how' to collect but not 'what' outcomes to measure and report. Although it is essential to provide definitions of outcomes, guidance is needed on what outcomes to collect. One approach to help standardise outcome measurement and reporting is using a systematically developed Core Outcome Set (COS). A COS is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care.[20] In this process, key stakeholders are consulted to ensure that clinically relevant and patient-relevant outcomes are identified and reported. The Core Outcome Measures for Effectiveness Trials (COMET) Initiative (www.comet-initiative.org) provides guidance on COS development and provides a database for ongoing COSs.

This study aimed to develop a COS for randomised controlled trials (RCTs) evaluating the effectiveness of interventions for the treatment of pregnant women with PGDM.

Methods

Ethical approval for this study was granted by the Clinical Research Ethics Committee, Galway University Hospitals, Galway, Ireland (Ref: C.A 2293). The study was registered prospectively with the COMET database (http://www.comet-initiative.org/studies/details/1425). The systematic review component of the study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173549). A detailed study protocol prepared in line with the COS-STAndardised Protocol Items Statement recommendations[21] has been published elsewhere.[22]

This study consisted of three components:

1 A systematic literature review to identify a list of all outcomes reported in prior or ongoing RCTs of interventions for the treatment of pregnant women with PGDM.
2 A three-round eDelphi survey where key stakeholders prioritised these outcomes.
3 A consensus meeting where a list of core outcomes was finalised to form the COS.

Systematic review

Data sources and searches

The following databases were searched for RCTs evaluating the effectiveness of interventions in pregnant women with PGDM; CENTRAL (via the Cochrane Library), Web of Science Medline (via OVID platform), Cumulative Index of Nursing and Allied Health Literature (via EBSCO host platform) and Embase. ClinicalTrials.gov and references were checked for studies not captured in the search. A combination of keywords and Medical Subject Headings (MeSH) terms were used to search for specific concepts. They were then combined using Boolean operators to formulate the

final search strategy. A sample search strategy is shown in Table S1.

Study selection

We included any RCT assessing outcomes of treatment interventions in pregnant women with PGDM reported in English. Two reviewers (OK and DB) independently screened titles and abstracts of the selected studies to ensure eligibility. Disagreements were resolved through discussion and recourse to a third author (FD) if necessary. Full-text papers of selected studies were reviewed by both reviewers before the final decision regarding inclusion.

Data extraction

All reported outcomes were extracted from the Methods and Results sections of the papers. A sample of the extraction template is shown in Table S2.

Data synthesis and analysis

Outcomes were grouped into maternal, fetal/neonatal and other. The study advisory group (SAG) including women with PGDM (CM and CO), healthcare professionals (HCPs) and researchers (OK, DB, PMO, LB, DD and FD) then reviewed the outcomes and further grouped them into the following domains: maternal (blood/urine parameters and monitoring, complications, life impact/psychological, miscellaneous), fetal/infant (laboratory measures, biometrics and anthropometrics, complications, miscellaneous) and other.

eDelphi study process

A three-round eDelphi survey was completed using the SurveyMethods software (https://surveymethods.com/). During this process, stakeholders were asked to rate outcomes for inclusion into the COS.

Stakeholders

Stakeholders were an international group of participants, including women and their representatives, HCPs, researchers and policy-makers. Women were recruited via email, face to face and through social media. We recruited HCPs, researchers and policy-makers with experience in the care of women with PGDM via email and social media. The leads of national and international organisations involved in the care of women with PGDM were contacted by email to encourage the participation of their members. All who participated were also encouraged to forward the study invite to anyone they deemed to have expertise in any field of maternal diabetes. We sent reminder emails to all participants who did not complete the survey.

Online international eDelphi surveys

In the email invitation explaining the study, we provided a link to direct the stakeholders to the survey page. Participants were able to provide explicit consent to take part in the study before proceeding. All participants who consented to the study were asked to provide demographic information including name, gender, ethnicity, stakeholder group, country of residence and email address at each survey round. A list of outcomes grouped into domains was provided to participants who were asked to rate the importance of the outcome for inclusion in the COS using a nine-point Likert type scale with score 1 representing an outcome of least importance and 9 representing an outcome of critical importance. The unable to rate option was available for all the outcomes for those who were unable to decide on a particular outcome. Clinical terms were explained using plain English to help those unfamiliar with medical terms, particularly women and their representatives, better understand the outcomes.

On the first round, participants were asked to rate outcomes and include up to two outcomes they thought might have been omitted. They were also required to complete the survey within 4 weeks with reminder emails sent to those who had not completed the questionnaire within the first 2 weeks to reduce attrition rates. On completion of round 1, participants were sent their results in addition to those of their stakeholder group and the collective group to review.

All outcomes from round 1 were included in round 2. In addition, the unique outcomes suggested by at-least two participants in round 1 were included in the round 2 survey. Only participants who completed round 1 were invited to round 2. Outcomes satisfying the inclusion criteria in round 2 progressed to round 3. 'Consensus in' for any outcome was defined as ≥70% participants scoring 7 to 9 and <15% scoring 1 to 3. 'Consensus out' was defined as ≤50% participants scoring 7–9 in each stakeholder group. Outcomes that did not meet any of these criteria were labelled as 'no consensus'. Only outcomes labelled as 'consensus in' progressed to round 3. Stakeholders were sent their individual results in addition to those of their stakeholder group and the collective group to review.

Participants who completed rounds 1 and 2 were invited to complete round 3. Only outcomes labelled as 'consensus in' progressed to the consensus meeting. These outcomes were forwarded to the consensus meeting participants before the meeting to review.

Consensus meeting

An online consensus meeting was carried out on 1 October 2020 via Zoom (https://zoom.us/) to finalise the COS. The meeting was chaired by an experienced, non-voting facilitator (DD). The facilitator provided an overview of the study, introduced each outcome, provided a plain language explanation, and ensured that all participants had an opportunity to make their opinion heard during the discussions. The panel consisted of an international audience with broad expertise in clinical maternal diabetes and

research. Participants used a live poll within Zoom to vote anonymously on each outcome brought forward from round 3. Participants were asked to vote yes or no for each outcome for inclusion in the COS after an open discussion. An outcome was included in the final COS when ≥70% participants voted yes. Voting was repeated after further discussion for outcomes with a borderline score (e.g. 69% yes/31% no). To facilitate dissemination and usefulness, some outcomes were renamed if necessary.

Patient involvement

Women were invited to participate as part of the SAG before commencement of the study. In this role, women contributed to important aspects of the study. They reviewed all listed outcome plain English definitions before dissemination to the wider audience to ensure that outcomes were understood by non-medical participants. They were involved in participant recruitment, COS development and manuscript writing.

Results

Systematic review

The results of the systematic review are shown in Figure S1. Of the 1475 potentially relevant studies, 67[16,17,23–87] fulfilled the inclusion criteria (Table 1). Two hundred and ten outcomes were extracted from the studies. Following SAG review where similar outcomes were combined, duplicate outcomes were removed and outcome terminology was clarified, 131 unique outcomes (69 maternal, 61 fetal/infant and one other) were presented for the first round (Table S3).

eDelphi surveys

The first round was completed by 205 participants. One hundred and forty-eight (72.2%) of the participants were female. One hundred and twenty-three (60.0%), 36 (17.6%) and 46 (22.4%) participants identified as HCPs, researchers/policy-makers, and women with PGDM/representatives, respectively. HCPs were represented by clinical biochemists, diabetologists/endocrinologists, diabetes nurse specialists, dieticians, general practitioners, midwives, obstetricians, paediatricians and pharmacists. The country of residence and ethnicity distribution of participants for all three rounds are shown in Table S4. One hundred and sixty-two (79.0%), 19 (9.3%), 10 (4.9), 6 (2.9%), 6 (2.9%) and 2 (1.0%) participants were from Europe, North America, Australia & New Zealand, Asia, South America and Africa, respectively, in round 1.

Round 2 was completed by 174 participants, giving a retention rate of 85% from round 1. Six new outcomes were added to round 2 because they had been suggested by more than one participant in round 1, bringing the total number of outcomes for round 2 to 137 (Tables 2 and 3). These additional outcomes were cardiovascular complications, postpartum depression, diabetes burnout, duration of breastfeeding, offspring incidence of diabetes and out-of-pocket cost of treatment. One hundred and twenty-five (71.8%) participants were female. One hundred and twenty-one (69.5%), 14 (8.0%) and 39 (22.4%) participants identified as HCPs, researchers/policy-makers and women with PGDM/representatives, respectively.

Ninety-five percent (165/174) of the participants completed round 3. Eighty-one outcomes were brought forward from round 2. In round 3, 116 (70.3%), 13 (7.9%) and 36 (21.8%) of respondents identified as HCPs, researchers/policy-makers and women with PGDM/representatives, respectively. Sixty-two outcomes classified as 'consensus in' were brought forward to the consensus meeting.

Consensus meeting

The consensus meeting panel consisted of 26 voting participants and one non-voting facilitator. The voting participants were an international audience from all the stakeholder groups; HCPs (n = 21), researchers/policy-makers (n = 3) and with PGDM/representatives (n = 2). Most of the HCPs also identified as researchers. Of those who identified as HCPs, 11 were endocrinologists, six were obstetricians, and there was one each of midwife, paediatrician, neonatologist and chemical pathologist. Participants were based in Europe (n = 19), North America (n = 5) and Australia/New Zealand (n = 2).

Before voting on each outcome, participants were shown the results (graphical representation and percentages) of how that outcome had scored in round 3 by each stakeholder group and the group as a collective. Six outcomes had a borderline score on initial voting (i.e. 69% yes/31% no). These outcomes were discussed at length and voting was carried out again. Discussions were broadly centred around ease of measuring the outcome, consensus on definitions and overall clinical relevance and importance. All outcomes for inclusion in the COS were then discussed at the end of the meeting and any queries were discussed and addressed. A list of the final COS including 8 maternal and 11 fetal/neonatal outcomes is shown in Table 4.

Time above glycaemic target, time in range and duration of hypoglycaemia, although important, were felt to be applicable only to studies where continuous glucose monitoring data were available. It was recommended that these outcomes can be reported in continuous glucose monitoring studies in addition to this COS.

Some outcomes, although deemed important, were excluded from the COS. Polyhydramnios was excluded because it is typically considered a surrogate marker for adverse pregnancy outcomes, rather than an end point in itself. Progression of retinopathy was excluded because not all studies (especially those based in emerging economies)

Table 1. List of trials included in the systematic review

	Article
1	Ainuddin JA et al. (2015)[25]
2	Bartal MF et al. (2018)*[30]
3	Bartholomew ML et al. (2015)[27]
4	Beazley D et al. (2005)[31]
5	Berry DC et al. (2018)**[32]
6	Beyuo T et al. (2015)[33]
7	Brooten D et al. (2001)[34]
8	Burkart W et al. (1988)[35]
9	Caritis S et al. (1998)[36]
10	Carr KJE et al. (2004)[26]
11	Cordua et al. (2013)[37]
12	Demarini S et al. (1994)[38]
13	Di Biase N et al. (1997)[39]
14	Dieb AS et al. (2019)*[40]
15	Feghali MN et al. (2018)*[41]
16	Feig DS et al. (2017)[29]
17	Feig DS et al. (2016)**[42]
18	Finnegan C et al. (2019)**[43]
19	Forster DA et al. (2017)[44]
20	Garmy G et al. (2017)*[45]
21	Gray L et al. (2018)*[46]
22	Hanson U et al. (1984)[47]
23	Hayden T et al. (2012)[48]
24	Herrera KM et al. (2015)[49]
25	Hickman MA et al. (2013)[50]
26	Hod M et al. (2008)[51]
27	Hod M et al. (2014)[17]
28	Horvaticek M et al. (2017)[52]
29	Ibrahim MI et al. (2014)[53]
30	Incerpi MH et al. (2001)[54]
31	Jovanovic-Peterson L et al. (1992)
32	Kjos SL et al. (1993)[56]
33	Laatikainen L et al. (1987)[57]
34	Lin L et al. (2018)**[58]
35	Linden K et al. (2018)[23]
36	Manderson JG et al. (2003)[59]
37	Mathiesen ER et al. (2012)[60]
38	Mathiesen ER et al. (2007)[61]
39	McCance DR et al. (2010)[62]
40	Mimouni F et al. (1987)[63]
41	Min Y et al. (2014)[64]
42	Monincx WM et al. (1997)[65]
43	Mostello D et al. (2017)*[24]
44	Murphy HR et al. (2008)[66]
45	Murphy HR et al. (2011)[28]
46	Nachum et al. (1999)[67]
47	Ney D et al. (1982)[68]
48	Nor Azlin MI et al. (2007)[69]
49	Notelovitz M (1971)[70]
50	Perichart-Perera O et al. (2012)[71]
51	Persson B et al. (2002)[72]
52	Petrovski G et al. (2013)[73]
53	Polsky S et al. (2019)*[74]
54	Refuerzo JS et al. (2015)[75]
55	Ringholm L et al. (2018)*[76]
56	Rosenberg VA et al. (2006)[77]
57	Sacks DA et al. (2006)[78]
58	Secher AL et al. (2013)[79]
59	Stewart ZA et al. (2018)[16]
60	Stewart ZA et al. (2016)[80]
61	Varner MW (1983)[81]
62	Voormolen DN et al. (2018)[82]
63	Wen SW et al. (2018)[83]
64	Wojcicki JM et al. (2001)[84]
65	Wright TE et al. (2000)[85]
66	York R et al. (1997)[86]
67	Novo Nordisk (2017)*[87]

*Clinicaltrials.gov article.
**Protocol paper.

can measure this outcome and this would limit its acceptability. Neonatal intensive care unit admissions was excluded because of differences in criteria for admission of infants to neonatal intensive care units. Outcomes excluded because of the lack of universally agreed definitions included: glycaemic control and hypoxic–ischaemic encephalopathy. Severe maternal hypoglycaemia was favoured over maternal hypoglycaemia because the former is more clinically meaningful. The following outcomes were excluded because they were well below the inclusion threshold at the initial vote and although the meeting chair opened and encouraged discussion on each of these outcomes, no participant voiced a desire to include: HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, cardiovascular complications and Apgar (5 minutes). Excessive maternal weight gain during pregnancy was changed to maternal weight gain during pregnancy to encompass all weight changes during pregnancy including excessive and insufficient weight gain.

Discussion

Main findings

An international group of key stakeholders agreed on a 19-outcome COS for future studies evaluating interventions in pregnant women with PGDM. We hope that the systematic implementation of this COS will help to reduce outcome reporting heterogeneity and bias. This will help to build robust evidence synthesis and reduce research waste in this important topic.

Strengths and limitations

Outcomes reported in RCTs only, were used as the basis of our systematic literature review because the aim of the

Table 2. Maternal outcomes progression from round 2 of eDelphi to end of consensus meeting

Outcomes	Round 2 consensus →	Round 3 consensus →	Consensus meeting consensus
Blood/urine parameters and monitoring outcomes			
1. Trimester-specific fasting blood glucose	IN	IN	OUT
2. Trimester-specific pre-prandial blood glucose	IN	OUT	–
3. Trimester-specific post-prandial blood glucose	IN	OUT	–
4. Duration of hypoglycaemia	IN	IN	OUT
5. Trimester-specific C-peptide	OUT	–	–
6. Time above glycaemic target	IN	IN	OUT
7. Time above glycaemic target during labour	OUT	–	–
8. 24-hour urinary loss of glucose	OUT	–	–
9. Glycaemic control	IN	IN	OUT
10. Homeostatic model assessment – insulin resistance	OUT	–	–
11. Self-measured eight-point plasma glucose profile	OUT	–	–
12. Trimester-specific HbA1c	IN	IN	IN
13. HbA1c, change from baseline to last measured or as stated	IN	OUT	OUT
14. HbA1c, at the time of the birth of the baby	OUT	–	–
15. Maternal blood glucose levels following first three milk expressing episodes	OUT	–	–
16. Trimester-specific fructosamine	OUT	–	–
17. Fructosamine, change from baseline to last measured or as stated	OUT	–	–
18. Fructosamine level, at the time of the birth of the baby	OUT	–	–
19. Time in range	IN	IN	OUT
20. Glycaemic variability	IN	OUT	–
21. Proteinuria	IN	IN	OUT
Complications outcomes			
22. Ectopic pregnancy	OUT	–	
23. Miscarriage	IN	IN	IN
24. Pregnancy termination	OUT	–	–
25. Maternal hypoglycaemia	IN	IN	OUT
26. Severe hypoglycaemic events	IN	IN	IN
27. Nocturnal hypoglycaemia	IN	IN	OUT
28. Pharmacological induction of labour	OUT	–	–
29. Complications of labour induction	IN	IN	OUT
30. Antepartum haemorrhage	IN	OUT	–
31. Postpartum haemorrhage	IN	OUT	–
32. Polyhydramnios	IN	IN	OUT
33. Diabetic ketoacidosis	IN	IN	IN
34. Progression of retinopathy	IN	IN	OUT
35. Preterm prelabour rupture of membranes	IN	IN	OUT
36. Maternal adverse effects associated with the treatment	IN	IN	OUT
37. Maternal renal failure	IN	IN	OUT
38. Placental dysfunction	IN	IN	OUT
39. Pre-eclampsia	IN	IN	IN
40. HELLP (haemolysis, elevated liver enzymes, and a low platelet count) syndrome	IN	IN	OUT
41. Placenta praevia	OUT	–	–
42. Placental abruption	IN	IN	OUT
43. Pregnancy (gestational) -induced hypertension	IN	IN	IN
44. Worsening chronic hypertension	IN	IN	OUT
45. Pulmonary oedema	IN	OUT	–
46. Cardiovascular complications*	IN	IN	OUT
47. Excessive maternal weight gain during pregnancy**	IN	IN	IN
48. Maternal death	IN	IN	IN
49. Prolonged labour	OUT	–	–

Table 2. (Continued)

Outcomes	Round 2 consensus →	Round 3 consensus →	Consensus meeting consensus
50. Maternal infection	IN	OUT	–
51. Insulin treated in labour	IN	OUT	–
52. Maternal intensive care unit admission	IN	IN	OUT
53. Pulmonary embolus	IN	OUT	–
Life impact/psychological outcomes			
54. Improvement in maternal affect	OUT	–	–
55. Postpartum depression*	OUT	–	–
56. Improvement in fear of hypoglycaemia	OUT	–	–
57. Diabetes distress	OUT	–	–
58. Diabetes burnout*	OUT	–	–
59. Improved self-efficacy of diabetes management	OUT	–	–
60. Satisfaction with intervention	OUT	–	–
61. Health-related quality of life	OUT	–	–
62. Return to normal activities	OUT	–	–
63. Views and experiences of women	OUT	–	–
64. Successful breastfeeding	IN	OUT	–
65. Duration of breastfeeding*	OUT	–	–
Miscellaneous			
66. Trimester-specific insulin dose	IN	OUT	–
67. Insulin dose at time of birth of the baby	OUT	–	–
68. Compliance with intervention	IN	IN	OUT
69. Compliance with glucose testing	IN	IN	OUT
70. Number and/or duration of antepartum hospitalisation	OUT	–	–
71. Number and/or duration of postpartum hospitalisation	OUT	–	–
72. Onset of labour	OUT	–	–
73. Hypoglycaemic awareness	IN	IN	OUT

HbA1c, glycated haemoglobin.
*Outcome suggested by more than one participant in round 1.
**Outcome rephrased to 'maternal weight gain during pregnancy' at the consensus meeting.

study was to define a COS for RCTs. We chose to search for studies in the databases reported in the methods for the literature review because previous COS studies by our group in the area of maternal diabetes from these databases had yielded comprehensive results.[88,89] Limiting our search to the English language may have introduced selection bias; however, in round 1 of the eDelphi survey, we gave participants the opportunity to add outcomes that they felt were omitted from the extracted list.

From the systematic search, 210 outcomes were extracted from the literature. To limit respondent fatigue during the eDelphi surveys, the SAG combined similar outcomes and removed duplicates, resulting in 131 unique outcomes. There is very little guidance in the literature on how to define, extract, group and count trial outcomes.[90] Advice was sought from relevant professionals, e.g. neonatologist, to ensure that outcome definitions and grouping were appropriate.

The INSPIRED group believes in the importance of Patient and Public Involvement.[91] Therefore, women were involved in a number of important aspects of the study including being part of the SAG and the consensus meeting in addition to making up the second largest group of stakeholders in all rounds of the eDelphi survey.

There is currently no consensus on the ratio of patients to HCPs/researchers in both the eDelphi process and the consensus meeting. In this study, the consensus meeting was represented mainly by HCPs/researchers but also included two women with PGDM. This has the potential to introduce bias. However, during the consensus meeting, these women shared experiences of outcomes that were important to them. In doing so, the group took on board patients' unique point of view before voting.

There is also no consensus on the best way to facilitate patient participation in COS development. Work has been done to tease out ways of making COS development more meaningful and accessible for patients.[92] The COMET People and Patient Participation, Involvement and Engagement working group has been established within the initiative

Table 3. Fetal/infant and other outcomes progression from round 2 of eDelphi to end of consensus meeting

		Round 2 consensus →	Round 3 consensus →	Consensus meeting consensus
Fetal/infant outcomes				
Laboratory measures outcomes				
1.	Insulin antibodies in cord blood	OUT	–	–
2.	Cord insulin-like growth factor 1	OUT	–	–
3.	Cord insulin	OUT	–	–
4.	Cord C-peptide	OUT	–	–
5.	Glucose in umbilical vein	OUT	–	–
6.	Neonatal blood glucose	IN	IN	OUT
7.	First glucose level after birth	IN	IN	OUT
Biometrics and anthropometrics outcomes				
8.	Birthweight	IN	IN	IN
9.	Infant weight at 6 months	OUT	–	–
10.	Long-bone measurements	OUT	–	–
11.	Neonatal length	OUT	–	–
12.	Abdominal circumference	IN	IN	OUT
13.	Infant fat mass	OUT	–	–
14.	Infant lean mass	OUT	–	–
15.	Shoulder circumference	OUT	–	
16.	Head circumference	IN	IN	
Complications outcomes				
17.	Neonatal polycythaemia	OUT	–	–
18.	Intestinal perforation	OUT	–	–
19.	Necrotising enterocolitis	OUT	–	–
20.	Intraventricular haemorrhage	IN	OUT	–
21.	Periventricular leucomalacia	OUT	–	–
22.	Reduced fetal movement requiring hospitalisation	IN	OUT	–
23.	Stillbirth	IN	IN	IN
24.	Neonatal death	IN	IN	IN
25.	Neonatal infection	IN	IN	OUT
26.	Congenital malformations	IN	IN	IN
27.	Hypotension	OUT	–	–
28.	Hearing impairment	OUT	–	–
29.	Acute respiratory problems	IN	IN	OUT
30.	Apnoea	IN	IN	OUT
31.	Hypoxic ischaemic encephalopathy	IN	IN	OUT
32.	Chronic lung disease	OUT	–	–
33.	Neonatal oxygen and/or ventilatory support	IN	IN	OUT
34.	QTc prolongation	OUT	–	–
35.	Heart arrhythmia	OUT	–	–
36.	Shoulder dystocia	IN	IN	IN
37.	Birth trauma	IN	IN	OUT
38.	Feeding problems	OUT	–	–
39.	Large for gestational age	IN	IN	IN
40.	Fetal macrosomia	IN	IN	OUT
41.	Appropriate for gestational age	IN	IN	OUT
42.	Small for gestational age	IN	IN	IN
43.	Low birthweight	IN	IN	OUT
44.	Retinopathy of prematurity	IN	OUT	–
45.	Neonatal intensive care unit admissions	IN	IN	OUT
46.	Length of stay in neonatal intensive care unit	IN	IN	OUT
47.	Neonatal hyperbilirubinaemia	IN	IN	OUT

Table 3. (Continued)

		Round 2 consensus →	Round 3 consensus →	Consensus meeting consensus
48.	Seizures	IN	IN	OUT
49.	Neonatal hypocalcaemia	IN	OUT	–
50.	Preterm birth	IN	IN	IN
51.	Neonatal hypoglycaemia	IN	IN	IN
52.	Treated neonatal hypoglycaemia	IN	IN	OUT
53.	Offspring incidence of diabetes*	IN	OUT	–
Miscellaneous outcomes				
54.	Apgar 1 minute	IN	OUT	–
55.	Apgar 5 minutes	IN	IN	OUT
56.	Gestational age at birth	IN	IN	IN
57.	Mode of birth	IN	IN	IN
58.	Live birth	IN	IN	OUT
59.	Infant psychomotor development	OUT	–	–
60.	Infants receiving exclusive breast milk	OUT	–	–
61.	Length and/or duration of hospitalisation	IN	OUT	–
62.	Neonatal neurological optimality score	OUT	–	–
Other outcomes				
1.	Healthcare cost	OUT	–	–
2.	Out-of-pocket cost of treatment*	IN	OUT	–

*Outcome suggested by more than one participant in round 1.

Table 4. Final list of outcomes to be included in a COS of all future studies of treatment interventions in pregnant women with pregestational diabetes

Domain	Outcome
Maternal outcomes	Trimester-specific HbA1c
	Maternal weight gain during pregnancy*
	Severe hypoglycaemia
	Diabetic ketoacidosis
	Miscarriage
	Pregnancy-induced hypertension
	Pre-eclampsia
	Maternal death
Fetal/infant outcomes	Birthweight
	Large for gestational age
	Small for gestational age
	Gestational age at birth
	Preterm birth
	Mode of birth
	Shoulder dystocia
	Neonatal hypoglycaemia
	Congenital malformations
	Stillbirth
	Neonatal death

HbA1c, glycated haemoglobin.
*Rephrased from 'Excessive maternal weight gain during pregnancy'.

specifically focusing on the public's involvement and participation in the development of COSs.

Unique outcomes were scored by local and international stakeholders in an online eDelphi survey format to give equal voice to all stakeholders. The stakeholders had a variety of expertise in all areas of maternal diabetes. Another limitation in our study is that, although we sought to recruit participants internationally, a majority of the respondents were from Europe and North America, similar to other COSs.[93] Although this has not been formally evaluated, others have suggested translating surveys into different languages and having a facilitator engage with stakeholders (particularly patients) during the eDelphi process to improve engagement with low- and middle-income country participants.[94] However, the outcomes listed in the final COS (Table 1) are for the most part easily measured and recorded globally. This will make the COS globally applicable where studies performed in low- and middle-income countries can adapt the COS in addition to their specific outcomes of interest.

There is no consensus regarding study sample size appropriate for COS development. Previous COS work by our group involved 173 and 288 participants, respectively, after round 1.[88,89] In this study, we had 205 participants after round 1. There were low attrition rates between

rounds of the eDelphi survey (15% round 1 to 2 and 5% round 2 to 3).

All outcomes satisfying the inclusion criteria from round 3 of the eDelphi survey were brought forward to a consensus meeting where an international audience with expertise in this area of maternal diabetes participated in decision-making for the final COS. Adapting to the current social distancing measures in the setting of the coronavirus disease 2019 pandemic, we conducted a successful online consensus meeting. As the consensus meeting was made up of an international group in different time zones, communication and organisation were key in the weeks and days leading up to the meeting to find a suitable time for all. Anonymous voting during this time ensured that no single person was put under pressure to vote a certain way for any given outcome. The facilitator ensured that all voices were heard and detailed discussions informed voting.

Interpretation

Outcome reporting in the RCTs assessing treatment interventions in pregnant women with PGDM is heterogeneous regardless of the specific intervention under study. It should be emphasised that this COS was focused on what should be measured and/or reported and not on how it should be measured. A general plain English definition of each outcome was provided during both the eDelphi survey stage and the consensus meeting to assist those unfamiliar with medical terms to make informed decisions. This COS highlights the importance of a common language and is complementary to work by Feig et al., which provides a repository of a set of definitions for clinical outcomes in diabetes in pregnancy.[19]

Although this COS focused specifically on RCTs, it has relevance to other types of studies, audits and quality improvement projects. Researchers are also not limited to outcomes listed in the COS but can measure and report additional outcomes of particular relevance to their topic.[20] For example, although none of the maternal life impact and psychological outcomes were included in the COS, these are still important outcomes that need further research.

Apart from haemoglobin A1c measurement, all of the outcomes listed in the COS are primarily observational and so would not require additional resources.

The James Lind Alliance through the Diabetes and Pregnancy Priority Setting Partnership has formulated a list of ten questions chosen by patients and clinicians to prioritise future research in diabetes and pregnancy to deliver maximum value and impact. For diabetes in pregnancy, a significant number of these research questions will assess interventions to improve outcomes for both mother and baby. Hence, it is now timely to entrench this COS in the research to make meaningful comparisons between interventions in the future.

Conclusions

This is the first COS for studies evaluating the effectiveness of interventions for the treatment of pregnant women with PGDM. This COS, agreed upon by key stakeholders including women with diabetes, will enable greater comparison and evidence synthesis across future RCTs in this area of maternal diabetes. In addition, this COS will help to improve trial reporting and minimise research waste by prioritising the collection and reporting of outcomes that matter to all relevant stakeholder groups. We now call upon researchers, funders and journals to incorporate this COS into trials, thereby improving research in pregnant women with PGDM and ultimately the health of these women and their infants. The use of an online platform to conduct the consensus meeting is novel in this type of research but is likely to be used more commonly and has the ability for increased participation from low- and middle-income countries.

Disclosure of interests

OK has Sanofi through Royal college of Physicians Ireland (RCPI) (Fellowship grant); Astrazeneca (Meeting Chair). DB has Wellcome Trust Irish Clinical Academic Training (ICAT) Programme fellow. TPG has Novonordisk (Endo Meeting 2020; Endo Meeting 2021). EN has Member of DSMB for EMERGE (Randomised controlled trial of the effectiveness of metformin in addition to the usual care in the reduction of gestational diabetes effects) trial. MJAM has NHS Litigation Authority (Expert opinion); NovoNordisk (Chair for the Drug Monitoring committee for Expect Trial–Now completed). SG has Dutch National Health Council. AS has GO MOMs Study (NIDDK) PI support. All other authors have nothing to disclose.

Contribution to authorship

OK and DB conducted the literature review. OK, DB, CM, CO, AME, PMO, CN, LB, DD and FD contributed to participant recruitment, COS development (as part of the SAG) and manuscript writing. TPG, LC, SDC, EA, EW-O, CClarson, AS, FA, EN, ED, AN, CCrowther, SG, MRL, MJAM, PG, HdeV and AA contributed to participant recruitment, COS development and manuscript writing. All authors revised the manuscript critically for important intellectual content and approved the final version to be published. OK co-ordinated the study and is responsible for the integrity of the work as a whole.

Details of ethics approval

Ethical approval for this study was granted by the Clinical Research Ethics Committee, Galway University Hospitals, Galway, Ireland (Ref: C.A 2293).

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Data availability statement

Data available on request from the authors.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. PRISMA flowchart of selection of studies for systematic review.

Table S1. Sample search strategy from EMBASE (via EBSCOHOST platform) (searched up to 16 January 2020).

Table S2. Sample outcome extraction. (T2DM Type 2 diabetes mellitus, PIH Pregnancy-induced hypertension, PET Pre-eclampsia, BGL Blood glucose levels, NICU Neonatal intensive care unit, LGA Large for gestational age, SGA Small for gestational age, TTN Transient tachypnoea of the newborn, RDS Respiratory distress syndrome, BP Blood pressure).

Table S3. Outcomes included in eDelphi round 1 and percentage of participants scoring each outcome 7–9.

Table S4. Country of residence and ethnicity distribution of eDelphi survey participants. ■

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