

**A Core Outcome Set for the Treatment of Pregnant Women with
Pregestational Diabetes: An International Consensus Study**

A thesis submitted for degree of Doctor of Medicine to the School of Medicine,
College of Medicine, Nursing and Health Sciences, National University of Ireland
Galway.

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Table of Contents

Declaration.....	v
Abstract.....	vi
Contributions to Research.....	vii
Published Papers and Outputs Arising from this Work	viii
Published Papers	viii
Poster Presentation at International Meeting	ix
Oral Presentation at International Meeting	ix
Acknowledgments.....	x
Funding	xi
List of Tables	xii
List of Figures	xiii
List of Abbreviations	xiv
List of Authors and Affiliations	xvii
Chapter 1: Introduction.....	21
1.1 Diabetes Mellitus: Background.....	21
1.1.1 Definition of Diabetes Mellitus.....	21
1.1.2 Diagnosis of Diabetes Mellitus	21
1.1.3 Categories of Diabetes Mellitus.....	22
1.2 Pre-gestational Diabetes (PGDM)	24
1.2.1 Prevalence of PGDM	24
1.2.2 Pathophysiology of PGDM and Complications.....	24
1.2.3 Complications of PGDM	25
1.2.4 Interventions Available for Treatment of PGDM	26
1.3 Why This Study Was Done.....	28
1.3.1 Core Outcome Sets.....	28
1.3.2 The CROWN Initiative	29
1.4 Overview of Thesis Objectives	30
1.5 Outline of Thesis.....	30
Chapter 2: The Study Protocol.....	31
2.1 Chapter Introduction	31
2.2 Paper 1: Developing A Core Outcome Set for the Treatment of Pregnant Women with Pregestational Diabetes—A Study Protocol	31
2.3 Abstract.....	32
2.4 Background.....	33
2.4.1 Scope of the Core Outcome Set	34
2.4.2 Study Work Packages	34
2.5 Methods.....	36

2.5.1 Ethics.....	36
2.5.2 Step 1: Systematic Review and Identification of Previously Reported Outcomes	36
2.5.3 Step 2: eDelphi Survey Involving Key Stakeholders.....	38
2.5.4 Step 3: Consensus Meeting	42
2.6 Dissemination and Implementation	42
2.7 Conclusion	42
Chapter 3: The Systematic Review	43
3.1 Chapter Introduction	43
3.2 Paper 2: A Systematic Review on Outcome Reporting in Randomised Controlled Trials Assessing Treatment Interventions in Pregnant Women with Pregestational Diabetes.....	43
3.3 Abstract.....	44
3.4 Introduction.....	45
3.5 Methods.....	46
3.6 Results.....	47
3.7 Discussion.....	58
3.8 Conclusions.....	60
Chapter 4: The Final Core Outcome Set.....	61
4.1 Chapter Introduction	61
4.2 Paper 3: A Core Outcome Set for The Treatment of Pregnant Women with Pregestational Diabetes: An International Consensus Study.....	61
4.3 Abstract.....	62
4.4 Introduction.....	63
4.5 Methods.....	64
4.5.1 Systematic Review	64
4.5.2 eDelphi Study Process	65
4.5.3 Consensus Meeting	67
4.5.4 Patient Involvement	67
4.6 Results.....	67
4.6.1 Systematic Review.....	67
4.6.2 eDelphi Surveys	72
4.6.3 Consensus Meeting	74
4.7 Discussion.....	81
4.8 Conclusions.....	84
Chapter 5: Other Contributions.....	85
5.1 Chapter Introduction	85
5.2 Paper 4: A Core Outcome Set for Studies of Gestational Diabetes Mellitus Prevention and Treatment.....	85
5.2.1 Abstract.....	86

5.2.2 Introduction.....	87
5.2.3 Methods.....	87
5.2.4 Results.....	90
5.2.5 Discussion.....	102
5.3 Paper 5: Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review.....	106
5.3.1 Abstract.....	107
5.3.2 Core Outcome Sets: Background and Rationale.....	107
5.3.3. Methods.....	109
5.3.4 COS in Diabetes in Pregnancy: Existing Work.....	109
5.3.5 Key Stakeholders: The Role of PPI.....	112
5.3.6 Defining Priority Areas for COS Development.....	115
5.3.7 Scope and Representativeness of COS.....	115
5.7.8 Methodological Advances and Review of Existing COS.....	116
5.7.9 COS Dissemination and Uptake.....	118
5.7.10 Summary.....	120
Chapter 6: Discussion and Conclusions.....	121
Chapter Introduction.....	121
Chapter 2.....	121
Chapter 3.....	121
Chapter 4.....	122
Chapter 5.....	123
Future Directions.....	123
References.....	125
Appendix 1 Full Search Strategy for Paper 3 and 4 (A core outcome set for the treatment of pregnant women with pregestational diabetes: an international consensus study).....	137
Appendix 2 List of All Included Studies for Paper 4 (A core outcome set for studies of gestational diabetes mellitus prevention and treatment).....	141
Appendix 3 License Statement for Paper 1 (Developing a core outcome set for the treatment of pregnant women with pregestational diabetes—a study protocol).....	149
Appendix 4 License Statement for Paper 4 (A Core Outcome Set for Studies of Gestational Diabetes Mellitus Prevention and Treatment).....	150
Appendix 5 License Statement for Paper 5 (Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review).....	151

Declaration

I, Oratile Kgosidialwa, certify that this work is submitted to fulfil the requirement of the degree of Doctor of Medicine, at the National University of Ireland Galway (NUIG) in the School of Medicine, College of Medicine, Nursing and Health Sciences (CMNHS). This thesis is a record of my own work and has not been previously submitted for any other academic award in this University or in any other academic institution. I am the author of this thesis and the principal author of the three included papers. Contributions to others' work are included under 'Chapter 5: Other Contributions'. Parts of this article-based thesis have appeared in peer reviewed publications and presentations. All information sources are fully referenced. I have no conflict of interest pertaining to the subject matter of this work.

Abstract

Background

Meaningful comparisons between studies evaluating interventions of pregnant women with pre-gestational diabetes mellitus (PGDM) are limited due to the heterogeneity in outcome selection and reporting. The aim of this study was to develop a core outcome set (COS) for randomised controlled trials (RCTs) evaluating the effectiveness of interventions for the treatment of pregnant women with PGDM.

Research Design and 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.

Results

We extracted 131 unique outcomes from 67 records meeting the full inclusion criteria. Two hundred and five stakeholders completed round 1 of the eDelphi survey, of whom 174/205 (85%) and 165/174 (95%) completed rounds 2 and 3, respectively. Participants of the consensus meeting chose 19 outcomes for inclusion in the final COS: trimester specific HbA1c, maternal weight gain during pregnancy, severe maternal hypoglycaemia, diabetic ketoacidosis, miscarriage, pregnancy induced hypertension, pre-eclampsia, maternal death, birth weight, 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 comparisons between RCTs, allowing robust evidence synthesis. The COS will improve trial reporting and optimise research efficiency in studies assessing treatment of pregnant women with PGDM.

Contributions to Research

This thesis consists of five papers, three of which I (**OK**) am lead author and two, co-author. All the papers presented in this thesis have been published in peer-reviewed journals.

For the first paper (Chapter 2), **OK** is the lead investigator and contributed to study design and to the development of the protocol. DB, AE, PMO, LB, DD and FD contributed to study design and to the development of the protocol. All authors read and approved the final manuscript.

For the second paper (Chapter 3), all authors were members of the study advisory group (SAG) and participated in the formulation of the methodology for this review. **OK** and DB screened titles and abstracts and extracted all the outcomes from the literature. All authors reviewed the list of extracted outcomes. All authors revised the manuscript critically for important intellectual content and approved the final version for publication. **OK** co-ordinated the study and is responsible for the integrity of the work as a whole.

For the third paper (Chapter 4), **OK** and DB conducted the literature review. **OK**, DB, CM, CO, AME, PMO, CN, LB, DD, FD contributed to participant recruitment, COS development (as part of the SAG) and manuscript writing. TPG, LC, SDC, EA, EWO, C Clarson, AS, FA, EN, GD, AN, C Crowther, SG, MRL, MJAM, PG, HdeV, 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 for publication. **OK** co-ordinated the study and is responsible for the integrity of the work as a whole.

For the fourth paper (Chapter 5), AME, ST, CCr, DD, LMB, DB and FPD designed the study. AME analysed the data and drafted the initial manuscript. **OK** and all authors made substantial contributions to the acquisition and interpretation of data, revised the manuscript critically for important intellectual content and approved the final version for publication. AME is responsible for the integrity of the work as a whole.

For the fifth paper (Chapter 5), AME and DB conducted the literature review. DB, **OK**, LB, PMO, DD, and FPD contributed to the manuscript writing. CM and CO have expertise in COS development as patient representatives with a history of PGDM. They provided their personal experience of patient involvement (PPI) in COS development and contributed to the manuscript writing. All authors revised the manuscript critically for important intellectual content and approved the final version for publication. AME coordinated the writing of the manuscript and is responsible for the integrity of the work as a whole.

Published Papers and Outputs Arising from this Work

Published Papers

1. **Kgosidialwa O**, Bogdanet D, Egan A, O'Shea PM, Biesty L, Devane D, Dunne F; INSPIRED group. Developing a core outcome set for the treatment of pregnant women with pregestational diabetes-a study protocol. *Trials*. 2020 Dec 11;21(1):1017. <https://doi.org/10.1186/s13063-020-04910-1>.
2. **Kgosidialwa O**, Bogdanet B, Egan A, Newman C, O'Shea PM, Biesty L, McDonagh C, O'Shea C, Devane D, Dunne F. On behalf of the INSPIRED group. A systematic review on outcome reporting in randomised controlled trials assessing treatment interventions in pregnant women with pregestational diabetes. *BJOG*. 2021. <https://doi.org/10.1111/1471-0528.16842>.
3. **Kgosidialwa O**, Bogdanet D, Egan AM, O'Shea PM, Newman C, Griffin TP, McDonagh C, O'Shea C, Carmody L, Cooray SD, Anastasiou E, Wender-Ozegowska E, Clarson C, Spadola A, Alvarado F, Noctor E, Dempsey G, Napoli A, Crowther C, Galjaard S, Loeken MR, Maresh MJA, Gillespie P, de Valk H, Agostini A, Biesty L, Devane D, Dunne F; For the INSPIRED research group. A core outcome set for the treatment of pregnant women with pregestational diabetes: an international consensus study. *BJOG*. 2021. <https://doi.org/10.1111/1471-0528.16825>.
4. Egan AM, Bogdanet D, Griffin TP, **Kgosidialwa O**, Cervar-Zivkovic M, Dempsey E, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. *Diabetologia*. 2020 Jun;63(6):1120-1127. <https://doi.org/10.1007/s00125-020-05123-6>.
5. Egan AM, Bogdanet D, Biesty L, **Kgosidialwa O**, McDonagh C, O'Shea C, O'Shea PM, Devane D, Dunne FP; INSPIRED research group. Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review. *Diabetes Care*. 2020 Dec;43(12):3129-3135. <https://doi.org/10.2337/dc20-1621>.

Poster Presentation at International Meeting

52nd Annual Diabetic Pregnancy Study Group meeting. 4th September 2020. Meeting held virtually due to the COVID19 pandemic. Randomised controlled trials evaluating the effectiveness of interventions for the treatment of pregnant women with pre-gestational diabetes- A protocol for developing a core outcome set.

53rd Annual Diabetic Pregnancy Study Group meeting. 3rd September 2021. Meeting held virtually due to the COVID19 pandemic. A Core Outcome Set for the Treatment of Pregnant Women with Pregestational Diabetes: An International Consensus Study.

Oral Presentation at International Meeting

Accepted for an oral presentation for the *57th European Association for the Study of Diabetes (EASD) Annual Meeting* to be held on 28th September to 1st October 2021. A core outcome set for the treatment of pregnant women with pregestational diabetes.

Acknowledgments

This thesis would not have been possible without the guidance of my trainer and mentor, Professor Fidelma Dunne. I could not have wished for a more supportive and responsive mentor. Her enthusiasm for her craft is unmatched and even the pandemic could not stop her! I am looking forward to our continued collaborations.

A very special thank you to my GRC members (Professor Declan Devane, Dr Yvonne Finn and Professor Tim O'Brien) for their support over the last two years. A big thank you to Prof Declan Devane, for his recommendation to change course in the face of a pandemic to ensure that my work would still be meaningful and impactful.

I would also like to thank Ms Louise Carmody for going above and beyond, to help me complete this piece of work and others. She has not only been a great colleague but also a good friend. A big thank you to Diabetes Nurse Specialist, Ms Breda Kirwan for her input and support. Her work ethic and infectious enthusiasm got us all through one of the most challenging times. Thank you to all the staff in the Centre for Diabetes, Endocrinology and Metabolism in Galway University Hospital.

A very special thank you to Dr Aoife Egan for her input and help despite her own heavy workload. I would also like to thank all other members of the INSPIRED group (Dr Paula M. O'Shea, Dr Delia Bogdanet, Dr Linda Biesty and Dr Christine Newman) and the rest of my co-authors for their unwavering support. A big thank you to Ms Christine O'Shea and Ms Carmel McDonagh for help guiding this work from a patients' perspective. Thank you to Mr Eric McSpadden for ensuring that the global virtual consensus meeting ran smoothly. I would also like to thank the Librarian in Galway University Hospital, Ms Denise Duffy, for her assistance with the search strategy.

Thank you to the Royal College of Physicians Ireland (RCPI) and Sanofi pharmaceutical company for providing me with a fellowship grant to support this work.

Finally, a big thank you to my family and friends for always being supportive. Thank you to my mother, Olebeng, for always believing in me. A big thank you to my partner Steve for all the meals he cooked while I worked. My second family (the Guilfoyle's) and all my friends and family, too many to name individually, I will be eternally grateful for your support.

Thank you!

Funding

I was awarded a research scholarship through the RCPI sponsored by Sanofi pharmaceutical company. This fellowship grant was awarded to undertake a project titled ‘Abnormal glucose tolerance in women diagnosed with Gestational Diabetes Mellitus using the International Association of the Diabetes and Pregnancy Study Groups criteria 10-years after an affected index pregnancy compared to women with normal glucose tolerance in the same period’. However, due to the Covid-19 pandemic, ongoing participant recruitment to the study was not possible. Thus, with the agreement of the RCPI, my mentor, GRC committee and School of Medicine (NUIG) my project was changed to the work reported in this thesis.

List of Tables

Table 1.1 Criteria for the diagnosis of diabetes mellitus	22
Table 2.1 Search strategy selection criteria of RCTs assessing outcomes of treatment interventions in pregnant women with PGDM	37
Table 2.2 Delphi consensus definition.....	40
Table 3.1 Number of outcomes reported in each study	49
Table 3.2 Types of interventions reported in each study	50
Table 3.3 Data extraction template	52
Table 3.4 All outcomes extracted from the literature (N=210)	53
Table 3.5 Definitions and timepoints of the most reported maternal and fetal/neonatal complication.....	56
Table 4.1 Outcomes included in eDelphi round 1 and percentage of participants scoring each outcome 7-9	68
Table 4.2 Country of residence and ethnicity distribution of eDelphi survey participants	73
Table 4.3 Final list of outcomes to be included in a COS of all future studies of treatment interventions in pregnant women with pre-gestational diabetes.....	75
Table 4.4 Outcomes progression from round 2 of eDelphi survey to end of consensus meeting	76
Table 5.1 Outcomes included in e-Delphi round 1 and number and percentage of respondents giving each outcome a “high” score of 7-9.....	94
Table 5.2 e-Delphi round 1 participants	99
Table 5.3 List of GDM prevention and treatment outcomes carried forward from round 2 and their status following round three voting and discussion at the consensus meeting.....	100
Table 5.4 Final COS to be included in future GDM prevention and treatment research	102

Table 5.5 Summary of COS publications relevant to diabetes in pregnancy	111
Table 5.6 PPI in COS development: written feedback from representatives	115

List of Figures

Figure 2.1 Flowchart of work schedule	35
Figure 3.1 PRISMA flowchart of selection of studies	48
Figure 3.2 Reported outcomes listed according to frequency of reporting (n=67).....	57
Figure 5.1 Summary of the study work packages	88
Figure 5.2 PRISMA flow diagram of the systematic review	92
Figure 5.3 Selection of studies for systematic review	93
Figure 5.4 Typical steps toward COS development	111
Figure 5.5 Road map for COS implementation in the field of diabetes in pregnancy.....	118

List of Abbreviations

ADA	American Diabetes Association
ADIPS	Australian Diabetes in Pregnancy Society
APH	Antepartum Haemorrhage
BJOG	British Journal of Obstetrics and Gynaecology
BMI	Body Mass Index
BP	Blood Pressure
CBG	Capillary Blood Glucose
CDA	Canadian Diabetes Association
CENTRAL	Cochrane Central Register of Controlled Trials
CGM	Continuous Glucose Monitor
CINAHL	Cumulative Index of Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core Outcome Set
COS-STAP	Core Outcome Set-STANDARDISED Protocol Items
COS-STAR	Core Outcome Set-STANDARDS for Reporting
CROWN	CoRe Outcomes in Women's and Newborn Health
CSII	Continuous Subcutaneous Insulin Infusion
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPSG	Diabetes in Pregnancy Study Group
EASD	European Association for the Study of Diabetes
EBCOG	European Board and College of Obstetrics and Gynaecology
FIGO	International Federation of Gynaecology and Obstetrics
FPG	Fasting Plasma Glucose
GCK	Glucokinase
GDM	Gestational Diabetes Mellitus

GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes
HbA1c	Glycated Haemoglobin
HELLP	Haemolysis, Elevated Liver Enzymes and Low Platelets
HIV	Human Immunodeficiency Virus
HHS	Hyperosmolar Hyperglycaemic State
HNF1A	Hepatocyte Nuclear Factor 1-alpha
HNF1B	Hepatocyte Nuclear Factor 1-beta
HNF4A	Hepatocyte Nuclear Factor 4-alpha
HSE	Health Service Executive
HTN	Hypertension
ICU	Intensive Care Unit
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IDF	International Diabetes Federation
IGF-1	Insulin-like Growth Factor 1
INSPIRED	International collaboration for Studies in PREgnancy and Diabetes
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Haemorrhage
JLA	James Lind Alliance
LGA	Large for Gestational Age
MiTy	Metformin in Women with Type 2 Diabetes in Pregnancy
MODY	Maturity Onset Diabetes of the Young
NEC	Necrotising Enterocolitis
NGSP	National Glycohemoglobin Standardization Program
NGT	Normal Glucose Tolerance
NICU	Neonatal Intensive Care Unit
NUIG	National University of Ireland, Galway
OGTT	Oral Glucose Tolerance Test
OMERACT	Outcome Measures in Rheumatology
PCOS	Polycystic Ovarian Syndrome
PCR	Protein Creatinine Ratio
PICO	Population Intervention Comparator Outcome

PIH	Pregnancy Induced Hypertension
PET	Pre-eclampsia
PG	Plasma Glucose
PGDM	Pre-gestational Diabetes
PPC	Pre-pregnancy Care
PPG	Post-Prandial Glucose
PPH	Post-Partum Haemorrhage
PPI	Public and Patient Involvement
PPROM	Preterm Premature Rapture of Membranes
PROSPERO	International Prospective Register of Systematic Reviews
PSP	Priority Setting Partnerships
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
SAG	Study Advisory Group
SGA	Small for Gestational Age
SMBG	Self-Monitoring of Blood Glucose
TTN	Transient Tachypnoea of the Newborn
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organisation
WOMBAT	WOMen and Babies Health and Wellbeing: Action Through Trials
WOS	World of Science

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Chapter 1

Chapter 1: Introduction

1.1 Diabetes Mellitus: Background

1.1.1 Definition of Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both¹. DM is associated with multiple complications resulting from both acute and chronic hyperglycaemia.

1.1.2 Diagnosis of Diabetes Mellitus

The current diagnostic criteria for DM distinguish a population with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications². At the time of diagnosis, patients with DM may fit into the following categories: asymptomatic, acutely symptomatic or symptomatic of chronic hyperglycaemia complications. Asymptomatic patients may be diagnosed when presenting for unrelated medical attention with an illness or during screening. The American Diabetes Association (ADA) recommends screening the following individuals for DM: overweight or obese (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) with \geq one risk factor(s) (hypertension (HTN), abnormal cholesterol levels, a history of polycystic ovary syndrome (PCOS), cardiovascular disease (CVD) or other clinical conditions associated with insulin resistance, physical inactivity, high-risk ethnicity and first degree relative with DM), Human Immunodeficiency Virus (HIV) infection, age ≥ 45 years, patients with prediabetes and women with a prior diagnosis of gestational diabetes mellitus (GDM)³.

Currently, DM diagnostic tests include the following: 1) fasting plasma glucose (FPG) 2) two-hour plasma glucose during the oral glucose tolerance test (OGTT) 3) random plasma glucose in the presence of signs and symptoms of DM and 4) glycated haemoglobin (HbA1c). A diagnosis of DM can be made based on any one of the criteria shown in Table 1.1³. In a patient without classic DM symptoms, diagnosis requires two abnormal test results.

Chapter 1

Table 1.1 Criteria for the diagnosis of diabetes mellitus

Measure	Diabetes Diagnosis	Notes
Random PG	≥ 11.1 mmol/L	In a patient with classic symptoms of hyperglycemia (polyuria, polydipsia or weight loss) or hyperglycaemic crisis (HHS or DKA).
FPG	≥ 7.0 mmol/L	Fasting is defined as no caloric intake for at least 8 hours.
2h PG	≥ 11.1 mmol/L	After a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
HbA1c	≥ 48 mmol/mol (6.5%)	Performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

PG Plasma glucose, HHS Hyperosmolar hyperglycaemic state, DKA Diabetic ketoacidosis, FPG Fasting plasma glucose, HbA1c Glycated haemoglobin, NGSP National Glycohemoglobin Standardization Program, DCCT Diabetes Control and Complications Trial.

1.1.3 Categories of Diabetes Mellitus

All forms of DM are characterised by hyperglycaemia and some form of beta (β) cell (pancreatic cell that synthesise and secrete insulin) dysfunction. Differences in DM are due to pathophysiology and aetiology. It is important to classify DM as it has implications for treatment strategies, prognosis and research. DM can be broadly classified into the following categories: Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), monogenic diabetes and other specific forms of diabetes⁴. Diabetes is a global health issue and it is estimated that by the year 2030, 578 million people globally will be living with diabetes⁵.

Type 1 Diabetes

T1DM is characterised by pancreatic β -cell destruction, typically leading to absolute insulin deficiency. This type of DM is for the most part due to cellular-mediated autoimmunity and accounts for 5-10% of DM cases⁶. In a small subset of patients with T1DM (commonly of African or Asian ancestry), there is no demonstratable cell mediated immune autoimmune destruction of the β -cell. These patients are prone to intermittent ketoacidosis and show varying degrees of insulin deficiency⁶. This type of DM is also known as Ketosis-Prone Diabetes or Flatbush Diabetes.

Chapter 1

Type 2 Diabetes

T2DM accounts for the majority of diabetes worldwide (90-95%)⁶. This form of diabetes is characterised by β -cell dysfunction in addition to varying forms of insulin resistance. The prevalence of T2DM is increasing globally in part due to increasing rates of obesity, sedentary lifestyle, aging population and dietary changes⁷.

Gestational Diabetes Mellitus

GDM is defined as diabetes first diagnosed during pregnancy that is not clearly overt diabetes. GDM is characterised by underlying β -cell dysfunction and insulin resistance particularly in the second and third trimesters. GDM is associated with adverse pregnancy outcomes in the short term. It is also associated with an increased risk of developing T2DM in both mother and offspring later in life^{8, 9}. The prevalence of GDM varies globally (2% to 45%)^{10, 11} owing in part to lack of global consensus on the screening and diagnostic criteria for GDM. Risk factors associated with developing GDM include obesity, increasing maternal age, family history of T2DM, prior history of GDM and non-white ethnicities.

Monogenic Diabetes

Monogenic diabetes is caused by mutation in a single gene resulting in β -cell loss or dysfunction and accounts for up to 5% of all diabetes³. Monogenic diabetes which can be inherited in an autosomal dominant or autosomal recessive fashion, can be broadly classified into Maturity Onset Diabetes of the Young (MODY), neonatal diabetes and mitochondrial diabetes. MODY usually presents in youth and adults and is commonly due to mutations in the transcription factors: hepatocyte nuclear factor 1-alpha (HNF1A), 4-alpha (HNF4A), 1-beta (HNF1B) and the enzyme, glucokinase (GCK)¹². Neonatal diabetes usually presents before six months of life and can be categorised into permanent and transient neonatal diabetes¹³. Mitochondrial diabetes is due to mutations in mitochondrial DNA, is maternally inherited and is associated with deafness¹⁴. Mitochondrial diabetes tends to be progressive and treatment with metformin is contraindicated due to risk of lactic acidosis¹⁴.

Other types of diabetes

Other less common forms of diabetes include post-transplant diabetes, diabetes associated with diseases of the exocrine pancreas (e.g. hereditary haemochromatosis, cystic fibrosis related diabetes and pancreatitis), diabetes associated with other endocrine diseases (e.g. Cushing's

Chapter 1

disease and acromegaly) and drug or chemical induced diabetes (e.g. atypical antipsychotics and protease inhibitors).

This thesis focuses on treatment interventions in pregnant women with pre-gestational diabetes mellitus (PGDM).

1.2 Pre-gestational Diabetes (PGDM)

PGDM, also called pre-existing diabetes, is defined as diabetes existing before pregnancy. The most common types of diabetes existing prior to pregnancy include type 1 (T1DM) and type 2 diabetes (T2DM).

1.2.1 Prevalence of PGDM

PGDM is one of the commonest chronic illnesses in pregnancy affecting 1% of pregnancies in low-risk cohorts¹⁵ and 4% in high-risk populations¹⁶. The prevalence of PGDM has also increased significantly in part due to the increasing obesity epidemic and increasing maternal age¹⁷. Type 2 diabetes (T2DM) accounts for the majority of the cases¹⁷. There are some ethnic variations in the prevalence of PGDM, with pre-gestational T2DM mostly prevalent in non-White populations and pre-gestational T1DM in White populations¹⁸.

1.2.2 Pathophysiology of PGDM and Complications

During pregnancy, significant alterations in maternal metabolism occur to ensure adequate supply of nutrients to the developing fetus. Glucose, the main source of energy for the fetus during development, is transferred from mother to fetus via the glucose-1 (GLUT-1) transporter¹⁹. Maternal insulin (both endogenous and exogenous) does not cross the placenta. Glucose crosses the placenta from mother to fetus down a concentration gradient. The fetal pancreas produces insulin as early as 10 weeks gestation²⁰.

To facilitate glucose supply to the fetus, there is an increase in maternal insulin sensitivity in early pregnancy to promote adipose tissue accretion followed by an increase in maternal insulin resistance in late pregnancy^{21, 22}. Insulin resistance in the latter part of pregnancy is facilitated by an increase in pregnancy related hormones such as progesterone and human placental lactogen²². Levels of pregnancy related hormones rise linearly throughout the trimesters of pregnancy such that by the second and third trimester, there is a nearly 50% decrease in insulin mediated glucose disposal²².

Chapter 1

These metabolic changes result in a lower fasting glucose in the early part of pregnancy compared to the non-pregnant state. In contrast, the latter part of pregnancy is characterised by increased postprandial hyperglycaemia due to absolute and relative maternal insulin deficiency in T1DM and T2DM respectively. This maternal postprandial hyperglycaemia results in fetal hyperglycaemia and fetal hyperinsulinemia. Increased fetal insulin production results in increased fetal fat deposition and skeletal growth and subsequent fetal macrosomia. The Danish epidemiologist Jorgen Pedersen, described the hyperglycaemic-hyperinsulinemia hypothesis, also known as the Pederson hypothesis in the 1950s as the underlying pathology for fetal macrosomia associated with diabetes in pregnancy²³. In this theory he states that *‘maternal hyperglycaemia results in foetal hyperglycaemia and, hence, in hypertrophy of foetal islet tissue with insulin hypersecretion. This again means a greater foetal utilization of glucose. This phenomenon will explain several abnormal structure and changes found in the newborn’*²⁴. This hypothesis has been confirmed in several studies^{25, 26}. The hyperglycaemia and adverse pregnancy outcomes (HAPO) study, a large international study of 25,505 pregnant women without overt diabetes, showed a linear relationship between increasing maternal glucose and cord C-peptide with birth weight above the 90th centile²⁶.

More recently, insulin resistance during pregnancy especially in the setting of obesity has been linked to inflammatory cytokine production by macrophages in the adipose tissue affecting post receptor insulin signalling²⁷.

The overarching cause of significant morbidity during a pregnancy affected by PGDM is fetal macrosomia and its complications.

1.2.3 Complications of PGDM

PGDM is associated with excess maternal and fetal/neonatal morbidity compared to women with normal glucose tolerance (NGT) in both the short- and long-term. In 1989, experts from the World Health Organisation (WHO) and International Diabetes Federation (IDF) convened in Italy to make recommendations for five-year targets in relation to people living with diabetes (the Saint Vincent Declaration). One of these targets, that pregnancy outcome in a woman with diabetes should approximate that of a woman without diabetes has not been reached, more than 30 years later²⁸. Adverse pregnancy outcomes associated with PGDM and long-term sequelae for the infant are discussed below.

Chapter 1

Short-term Complications of PGDM

PGDM is associated with the following adverse neonatal outcomes: macrosomia/large for gestational age (LGA), shoulder dystocia, neonatal trauma, congenital malformations, caesarean section birth, preterm birth, stillbirth, hypoglycaemia, respiratory distress, jaundice, requirement for neonatal intensive care unit (NICU) admission and recurrent miscarriages^{16, 29-32}. In addition, mothers have a higher risk of comorbid illnesses during pregnancy such as pre-eclampsia (PET), pregnancy induced hypertension (PIH), diabetic retinopathy and worsening of diabetic kidney disease^{29, 33}.

Long-term Complications of PGDM

Children born to women with PGDM are at increased risk of diabetes, obesity and cardiovascular disease³⁴ beginning in early childhood. Diabetes in the offspring appears to be caused by a combination of hyperglycaemia in utero and genetic susceptibility. The diabetic intrauterine environment has been shown to result in metabolic programming and epigenetic modifications in the offspring³⁵. This interplay between genetics and the intrauterine environment has been shown in some studies, where siblings born to mothers after a diagnosis of diabetes were at a higher risk of developing T2DM and obesity compared to siblings born before maternal diabetes³⁶.

Although controversial, there is also some evidence to suggest an association between maternal diabetes and poor cognitive development in the offspring³⁷. The evidence to support this association largely comes from observational studies. One study found that although non-sibling offspring of women with diabetes were more likely to have a lower cognitive ability, no such association existed between sibships³⁸.

1.2.4 Interventions Available for Treatment of PGDM

PGDM poses a significant healthcare and economic burden. As a result, there have been advancements in treatment interventions to reduce the burden of disease for both mother and baby. These interventions can be broadly categorised in to pre-pregnancy care (PPC), education, technology and pharmacology.

Pre-pregnancy care (PPC)

PPC aims to promote the health of women of reproductive age before conception by amending lifestyle, behavioural, medical, and social risks to a woman's health or pregnancy³⁹. The main goal of PPC is to improve pregnancy outcomes. In women with PGDM poor glycaemic control

Chapter 1

at conception is associated with an increased risk of congenital malformations⁴⁰ and perinatal mortality⁴¹. PPC for women with PGDM has been shown to improve pregnancy outcome and to be cost effective⁴²⁻⁴⁴.

Educational Interventions

Patient education has long been recognised as the cornerstone of self-care in diabetes. In the general diabetes population, patients who are empowered and skilled to manage their diabetes have better outcomes⁴⁵. In PGDM, education programs including intensive insulin management have been shown to improve glycaemic control during pregnancy⁴⁶. Other programs such as text messaging for diabetes support and education during pregnancy have been shown to improve diabetes self-care activities⁴⁷.

Technological Interventions

Technological advances in the general diabetes population have increased over the last number of years. Some technological advancements used in pregnancy include continuous glucose monitoring (CGM), closed-loop insulin delivery systems and insulin pumps and have been shown to improve glycaemic control during pregnancy⁴⁸ and pregnancy outcomes⁴⁹.

Pharmacological Interventions

The mainstay of PGDM treatment is insulin and metformin. All patients with T1DM are treated with insulin. Patients with T2DM may receive the oral agent metformin, or insulin or both depending on local guidelines. Metformin is a biguanide whose mechanism of action is not completely clear but has been shown to reduce hepatic gluconeogenesis and improve insulin sensitivity by increasing peripheral glucose uptake and utilisation⁵⁰. Although metformin crosses the placenta it appears to be safe, at-least in the short term. The use of metformin in pregnant patients with T2DM has been associated with reduced maternal weight gain and insulin dosage, improved maternal glycaemic control and reduced rates of LGA⁵¹. The risk of small for gestational age (SGA) infants as a result of metformin exposure remains controversial. A systematic review of RCTs assessing the effects of metformin use in pregnancy in women with both GDM and T2DM found no increased risk⁵². However, a RCT of metformin compared to insulin use in pregnant patients with T2DM (MiTy trial) found an increased risk of SGA⁵³.

Chapter 1

Long-term effects on the offspring as a consequence of metformin remain controversial⁵². Follow-up data largely comes from observational studies or studies of metformin use in polycystic ovarian syndrome (PCOS) and GDM⁵⁴. In a systematic review assessing long-term effects (up to 13 years of age) of metformin, children exposed to metformin were more likely to be heavier than those who were not exposed⁵⁴. In another systematic review of metformin use during a pregnancy affected by GDM, neonates with prenatal exposure were more likely to be smaller but by mid-childhood they were heavier compared to the insulin group⁵⁵.

Maternal endogenous insulin does not cross the placenta⁵⁶. Human insulins (soluble insulin and Neutral Protamine Hagedorn) were the gold standard treatment for pregnant women with PGDM for many years because of low antigenicity, minimising transplacental transport of insulin antibodies seen with animal insulins. Insulin analogues (both rapid- and long-acting) are now widely used after evidence from RCTs showed that they were safe to use in pregnancy⁵⁷⁻⁵⁹. RCTs on newer insulins (ultra-long acting⁶⁰ and faster acting analogues⁶¹) use in pregnancy are currently underway.

Finally, pregnant women with PGDM are classified as high-risk pregnancies, thus are included in studies evaluating treatment/ preventive interventions for other comorbidities more likely to develop in such pregnancies. One such example is treatment interventions (e.g. aspirin, vitamins) to prevent PET⁶²⁻⁶⁴.

1.3 Why This Study Was Done

There exists an extensive variety of maternal and fetal/infant outcomes that are reported in the literature. The number of interventions in diabetes in pregnancy will continue to increase over time as the community strives towards achieving the St Vincent Declaration for women living with diabetes. It will thus be imperative to synthesis robust data around their efficacy. Currently outcome definition and reporting in the area of maternal diabetes is heterogenous making data synthesis on the efficacy of interventions difficult⁶⁵ and thus limiting recommendations for clinical practice. Some work has been done to address outcome definitions⁶⁵ and standardisation of outcome reporting through the creation of Core Outcome Sets (COS) to address heterogeneity in outcomes measured.

1.3.1 Core Outcome Sets

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*⁶⁶. COSs are created in

Chapter 1

recognition of issues in outcome selection, measurement and reporting in clinical trials. Development of a COS involves identifying all potential outcomes related to the subject of interest, then engaging a wide range of stakeholders including patients and healthcare providers to rank the outcomes for inclusion into the core set of outcomes to be reported in future clinical trials.

One of the earlier initiatives to standardise outcome reporting was in 1979 by WHO for the reporting of results in cancer treatment⁶⁷. This initiative however, did not include patients as stakeholders. The most notable work on COS development has been in the field of rheumatology by the Outcome Measures in Rheumatology (OMERACT) collaboration⁶⁸. Although this work did not initially involve patients as key stakeholders, the value of their input was recognised and has served as a template for current COS development. The aim of a COS is to reduce selective and heterogenous outcome reporting. In addition, COSs ensure that trials report outcomes that are clinically meaningful. Researchers are not limited to reporting only on outcomes in the COS but are free to choose their own outcome of interest in addition to those listed in the COS⁶⁶.

The Core Outcome Measures in Effectiveness Trials (COMET) initiative was launched in 2010 to bring together people interested in the development and application of COSs (<https://www.comet-initiative.org/>). To avoid unnecessary duplication of work, COMET has set up a database where COSs can be registered. In addition, the initiative also provides guidance on protocol development (Core Outcome Set-STANDARDISED Protocol Items: COS-STAP)⁶⁹ and the reporting of COS studies (Core Outcome Set-STANDARDS for Reporting: The COS-STAR)⁷⁰.

1.3.2 The CROWN Initiative

In the area of maternal diabetes, the CoRe Outcomes in Women's and Newborn health (CROWN) initiative (<http://www.crown-initiative.org>) was developed to harmonise outcome reporting in women's health research⁷¹. The initiative was created in recognition of outcome reporting inconsistencies in the literature, with editors of over fifty journals coming together to support the CROWN initiative.

This thesis will add to this initiative by developing a COS for trials evaluating treatment interventions in pregnant women with PGDM.

Chapter 1

1.4 Overview of Thesis Objectives

The primary objective of this thesis, is the development of a COS for future trials assessing treatment interventions in pregnant women with PGDM. The COS development involves the following steps:

- a) Performing a systematic review where all outcomes reported in RCTs assessing treatment interventions in pregnant women are extracted and collated.
- b) Presenting this list of outcomes to key stakeholders to rank for inclusion into the COS through an iterative eDelphi survey process.
- c) A global virtual consensus meeting where key stakeholders meet to finalise a list of outcomes for inclusion into the COS.
- d) Publication of the Protocol, Systematic Review and COS in international peer reviewed journals.

1.5 Outline of Thesis

Chapter 2 presents the methodology of the COS development as a detailed study protocol.

Chapter 3 presents the systematic review process.

Chapter 4 presents the results of the COS development process and the final COS.

Chapter 5 presents contribution to others' work.

Chapter 6 presents a discussion of the thesis and contribution to current knowledge.

Chapter 2

Chapter 2: The Study Protocol

2.1 Chapter Introduction

This chapter presents paper 1: The study protocol for developing a core outcome set for future studies evaluating treatment interventions in pregnant women with pregestational diabetes. The methodology for the development of the COS is outlined in this chapter.

2.2 Paper 1: Developing A Core Outcome Set for the Treatment of Pregnant Women with Pregestational Diabetes—A Study Protocol

Kgosidialwa O, Bogdanet D, Egan A, O'Shea PM, Biesty L, Devane D, Dunne F; INSPIRED Research group. Developing a core outcome set for the treatment of pregnant women with pregestational diabetes- a study protocol. Trials. 2020 Dec 11;21(1):1017. <https://doi.org/10.1186/s13063-020-04910-1>.

Chapter 2

2.3 Abstract

Background Pre-gestational diabetes mellitus (PGDM) is associated with adverse pregnancy outcomes including increased rates of caesarean section birth, macrosomia, congenital malformations, prematurity, admission to the neonatal intensive care unit (NICU) and stillbirth. As a result, there has been an increase in interventions to improve outcomes in both mother and infant. To date, meaningful comparisons between these studies are limited due to heterogeneity in outcome selection and reporting. The aim of this study is to develop a core outcome set (COS) for randomised controlled trials (RCTs) evaluating the effectiveness of interventions for the treatment of pregnant women with PGDM.

Methods The study consists of three steps. The first step is a systematic review of the literature to assess outcomes reported in RCTs assessing the effectiveness of interventions for the treatment of pregnant women with PGDM. The second step is a three round, online Delphi survey to prioritise these outcomes. In this step, stakeholders (including women with PGDM, healthcare workers, researchers and policymakers) will be asked to rank the importance of outcomes for inclusion in the COS using a 9-point Likert type scale. Outcomes that meet the inclusion criteria after completion of the Delphi surveys will be brought to the consensus meeting. The consensus meeting will be the third and final step, where the COS will be finalised. The consensus meeting will include members from each stakeholder group.

Discussion: This paper describes the process used to develop a COS for the reporting of studies evaluating the effectiveness of interventions in pregnant women with PGDM. The COS will enable greater comparison between and information synthesis across RCTs in the treatment of PGDM. In addition, this COS will also help improve trial reporting and minimise research waste by prioritising the collection and reporting of outcomes that matter to all relevant stakeholder groups.

Trial registration: This COS has been registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative (<http://www.comet-initiative.org/studies/details/1425>) on the 4th of November 2019. The systematic review component of this study has also been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration ID: CRD42020173549).

Chapter 2

2.4 Background

Pre-gestational diabetes mellitus (PGDM) is defined as diabetes existing prior to pregnancy (including type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)). The prevalence of PGDM ranges from 1% in a racially diverse community¹⁵ to 4.3% in high-risk populations¹⁶. The incidence of PGDM continues to increase¹⁷. There has been a sharp increase in recent years in the incidence of pre-pregnancy T2DM in parallel with the increasing global obesity pandemic especially in newly industrialised and emerging countries^{17, 72-74}. PGDM is associated with poor outcomes in women and their infants. These women are more likely to have induction of labour, to have a caesarean birth or have a birth complicated by shoulder dystocia^{16, 30, 75}. Additionally, these women are also vulnerable to pregnancy related comorbid conditions such as pre-eclampsia and pregnancy-induced hypertension^{31, 76}. New-borns of women with PGDM are more likely to display macrosomia, be born preterm, be admitted to the neonatal intensive care unit (NICU), have major congenital malformations or be stillborn^{16, 31, 77}. Pre-pregnancy maternal complications such as diabetic retinopathy³³ may also worsen for women with PGDM during pregnancy.

There have been continued efforts in education, technology and pharmacology to improve maternal and infant outcomes in women with PGDM. Technological advances including improved insulin delivery via continuous subcutaneous insulin infusion (CSII)⁷⁸, insulin analogues⁵⁹ and closed loop systems^{48, 79} have and continue to be examined for use by pregnant women with PGDM. Improved glucose testing techniques have also increased in the general diabetes population and some of these techniques have also been examined in pregnant populations, e.g. continuous glucose monitoring (CGM)⁴⁹ and flash glucose sensors⁸⁰. Internet and phone applications are emerging tools for self-care for women with PGDM^{81, 82}. There is evidence that advancements in technology, education and pharmacology have improved clinical outcomes for women with diabetes in pregnancy^{83, 84}. However, the way in which outcomes are reported often makes it difficult to compare the effects of interventions and robustly synthesise evidence⁶⁵. Thus, we will develop a core outcome set (COS) for randomised controlled trials (RCTs) assessing the effectiveness of interventions for the treatment of pregnant women with PGDM.

A core outcome set 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 care⁶⁶. The aim is to reduce reporting bias and heterogeneity of outcomes in order to support robust evidence

Chapter 2

synthesis. This process usually involves a wide variety of key stakeholders to ensure that clinically relevant outcomes are identified and reported.

2.4.1 Scope of the Core Outcome Set

The COS will be applicable to future RCTs evaluating the effectiveness of interventions for the treatment of pregnant women with PGDM. The COS may also be useful for studies beyond trials and for routine clinical practice. It is known that pre-pregnancy care (PPC) as an intervention in women with PGDM improves both maternal and neonatal outcomes⁴⁴. PPC is outside the scope of this work and will not be addressed in this project. A COS for PPC as an intervention has already been developed⁸⁵.

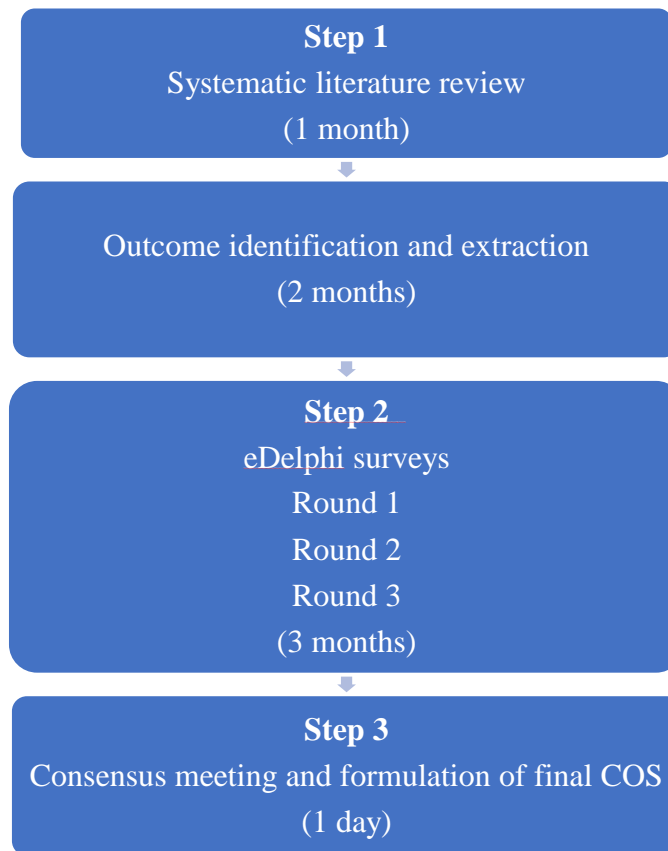
2.4.2 Study Work Packages

This study has 3 work packages (Figure 2.1):

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 e-Delphi survey where key stakeholders will prioritise these outcomes.
3. A consensus meeting where a list of core outcomes will be finalised and form the COS. The final core outcome set will be published in a scientific journal.

Chapter 2

Figure 2.1 Flowchart of work schedule



COS- core outcome set

Chapter 2

2.5 Methods

Preparation of this protocol is in line with the COS-STAP Statement recommendations which gives guidance on items considered essential in a COS protocol⁶⁹. Our methodology is similar to previous work our group has carried out in the development of COSs in other areas of maternal diabetes⁸⁷⁻⁸⁹. To date, we are not aware of any published COS of RCTs evaluating the effectiveness of interventions in pregnant women with PGDM. This COS has been registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative. (<http://www.comet-initiative.org/studies/details/1425>). The systematic review component of this study has also been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020173549).

2.5.1 Ethics

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

2.5.2 Step 1: Systematic Review and Identification of Previously Reported Outcomes

Systematic Review Question

What are the outcomes reported in RCTs evaluating the effectiveness of interventions in pregnant women with PGDM?

Population

Pregnant women with PGDM.

Interventions

Any intervention offered to the pregnant woman with PGDM will be included. Interventions can be broadly categorised into technological, pharmacological, lifestyle and educational.

Types of Studies

Randomised trials. Trials assessing outcomes in both PGDM and GDM in the same study will also be included. Longitudinal follow-up studies and secondary analysis of clinical trials will be excluded. Reviews, reports of conference proceedings or abstracts where there is no complete description of the trial methodology will also be excluded.

Chapter 2

Search Strategy and Information Sources

A search strategy will be formulated with the assistance of a librarian at the National University of Ireland, Galway (NUI Galway). A PICO format will be used to guide the search strategy (Table 2.1). A combination of keywords and Medical Subject Headings (MeSh) terms will be used to search for specific concepts, which will then be combined using Boolean operators to formulate the final search strategy.

Table 2.1 Search strategy selection criteria of RCTs assessing outcomes of treatment interventions in pregnant women with PGDM

Population	Pregnant women with pregestational diabetes
Intervention	Any intervention including education, lifestyle, pharmacology and technology
Comparator	Any comparator or control
Outcome	Any measured or reported outcome

RCTs- randomised controlled trial; PGDM-pregestational diabetes mellitus.

The following databases will be searched: CENTRAL (via the Cochrane Library), Web of Science (WOS), MEDLINE (via OVID platform), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (via EBSCO host platform) and Embase. In addition, ClinicalTrials.gov will be searched for ongoing trials. The references of clinical trials evaluating interventions in the treatment of pregnant women with PGDM will be checked for studies not captured in the search. Publications are restricted to those in English. There will be no time restrictions applied to the search strategy; however, the final search will be completed by the end of January 2020. The search strategy is shown in table Appendix 1.

Study Assessment

Studies deemed suitable for inclusion will be identified from the search using the predetermined inclusion criteria. Two independent reviewers (OK and DB) will screen titles and abstracts of the selected studies to ensure eligibility. Full-text papers of selected studies will be reviewed by both reviewers prior to final decision regarding inclusion. Disagreements will be resolved through discussion and recourse to a third author (FD) if necessary.

Chapter 2

Data Extraction

Outcomes for potential inclusion into the COS will be extracted from the ‘methods’ and ‘results’ section of each paper. We will then assess how each outcome was defined, instruments or indicators used to measure the outcome and the time points or periods of outcome measurement. In addition, a data extraction template consisting of the following parameters will be developed; authors, study design, condition of interest (T1DM, T2DM or both), journal and year of publication. Two independent reviewers (OK and DB) will assess the articles independently, review outcomes together and ensure that all outcomes have been identified and included.

Data Analysis

All eligible studies will be tabulated. Outcomes identified for inclusion will be listed and defined. Any differences in definitions of outcomes will be noted. All outcomes identified will be categorised into appropriate domains by the authors. The Study Advisory Group (SAG), involving healthcare workers, researchers and women with a history of PGDM will then review the outcomes and outcome domains and assess suitability of grouping of outcomes and titles of the domains.

2.5.3 Step 2: eDelphi Survey Involving Key Stakeholders

Stakeholders

Stakeholders in this COS will include women with a history of PGDM, clinicians, researchers and policy makers. The research team involved in this COS have diverse experience in both clinical maternal diabetes and COS research. There are 3 main stakeholder groups.

Group 1: Service Users

Women with PGDM who have been pregnant previously or are currently pregnant will be invited to participate. These women will be identified from a variety of sources. Women currently attending our antenatal or general diabetes clinics will be invited to participate face to face, via post or email. Clinical leads in other hospitals will also be contacted via email to invite women attending their service to participate. In addition, known diabetes service user group managers will be emailed to invite women to participate.

Chapter 2

Group 2: Clinicians and Researchers

An international cohort of clinicians and researchers will also be invited to participate in the COS. Clinicians will be invited to participate from all areas of care associated with pregnant women. This will include Diabetologists, Diabetes Nurse Specialists, Midwives, Dieticians, Obstetricians, Neonatologists, Paediatricians, Clinical Biochemists, General Practitioners, Practice Nurses, Occupational Therapists and Physiotherapists. Clinical leads of both national and international organisations involved in the treatment and/or research of women with PGDM will be identified and recruited. International organisations of specific interest include the Diabetic Pregnancy Study Group (DPSG), a study group of the European Association for the Study of Diabetes (EASD), the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the International Federation of Gynaecology and Obstetrics (FIGO), the European Board and College of Obstetrics and Gynaecology (EBCOG), the American Diabetes Association (ADA) the Canadian Diabetes Association (CDA) and the Australian Diabetes in Pregnancy Society (ADIPS). Clinical leads will be recruited via email and encouraged to invite participants from their pregnancy care teams.

Group 3: Policy Makers

National and international policy makers from the Health Service Executive (HSE), International Diabetes Federation (IDF) and World Health Organization (WHO) will be invited. All potential participants will be sent an invitation to participate in the study via email. The invitation will be in plain English where possible. Where medical terms are unavoidable, a lay description of the word or phrase will be given in parenthesis. This invitation will include the synopsis and aim of the study and a link to the online survey. Prior to commencing the survey at registration, participants will be explicitly required to provide informed consent. All those receiving the online invitation will be encouraged to also forward it to anyone they deem to have expertise in any field of maternal diabetes.

Online International eDelphi Surveys

A Delphi survey will be used to develop a consensus of the most important outcomes of interventions in women with PGDM identified from the systematic review. The Delphi is a group facilitation technique that seeks to obtain consensus on the opinions of ‘experts’ through

Chapter 2

a series of structured questionnaires (commonly referred to as rounds)⁹⁰. The rounds are a repetitive multistage process designed to combine opinions into group consensus⁹⁰.

After completion of the systematic review described in step 1, a long list of potential outcomes will be available. Clinical terms will be explained using plain English to help service users better understand outcomes. Outcomes will be grouped into domains. To avoid potentially weighting outcomes in the order with which they are displayed and introducing bias, outcomes will be randomly listed within the specific domains. Participants will rank importance of potential outcomes for inclusion in the COS using a 9-point Likert scale with a score of 1 representing an outcome of least importance and a score of 9 representing outcome of critical importance. This scale was formulated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group in order to help facilitate the ranking of outcomes according to their importance and has been used widely in the process of COS development⁹¹.

A prespecified consensus criteria which was previously used by our group, will be used to either include or exclude outcomes at the end of each round^{89, 92} (Table 2.2). In brief, ‘Consensus in’ for any outcome will be defined as $\geq 70\%$ participants scoring 7 to 9 and $< 15\%$ scoring 1 to 3. ‘Consensus out’ will be defined as $\leq 50\%$ participants scoring 7–9 in each stakeholder group and will be excluded. Outcomes that do not meet any of these criteria were labelled as ‘no consensus’. After each round of questions, an anonymous summary of the responses and participants’ own individual response will be reported back to the group. At this stage, participants may choose to keep their original responses or change their stance in the following round.

Table 2.2 Delphi consensus definition

Consensus decision	Definition	Scoring
Consensus in	Consensus that outcome should be included in the COS	$\geq 70\%$ participants scoring 7 to 9 AND $< 15\%$ scoring 1 to 3.
Consensus out	Consensus that outcome should be excluded in the COS	$\leq 50\%$ participants scoring 7-9 in each stakeholder group
No consensus	Uncertainty about importance of the outcome	Anything else not fitting criteria above for ‘consensus in’ or ‘consensus out’.

COS- Core outcome set⁹².

Chapter 2

Round 1

Upon consenting to participate in the online questionnaire as described above, participants will be requested to record their name, gender, country of residence, email address and centre they are affiliated with. In addition, they will be asked to identify the stakeholder group and subgroup to which they belong. Participants will be required to complete the survey within 4 weeks with up to two reminder emails to complete the questionnaire sent at least a week prior to closing the survey to reduce attrition rates. Participants will be invited to include any other outcomes that they think may have been missed which will be included in subsequent eDelphi surveys sent to participants. Participants will be limited to adding two potential outcomes only. Outcomes will be included in the subsequent eDelphi round if at least two participants have listed it as a possible outcome.

Round 2

The round 2 instrument will consist of all outcomes brought forward from round 1. Additional unique outcomes suggested by at least two participants in round 1 will be included in the round 2 survey with the outcomes progressing from round 1. All participants who completed round 1 will be invited to take part in round 2 of the eDelphi. All outcomes from round 1 including any new additional outcomes meeting the inclusion criteria will be included in round 2. As in round 1, outcomes will be presented with a 9-point Likert type scoring system. Participants will be presented with findings from the round 1 survey, i.e. the number of participants taking part, the proportion of people scoring each rating point on the Likert scale for each stakeholder group and the group overall and how their own scores compare to the rest of the group. Based on the feedback provided to participants after round 1, they will be asked to rate the outcomes again using the same 9-point scale as used in round 1. This will give participants the opportunity to change their scoring on outcomes based on the knowledge of what they and their stakeholder group scored in round 1.

Round 3

The round 3 instrument will consist of all outcomes classified as 'consensus in' brought forward from round 2. Only participants who completed round 1 and 2 will be invited to participate in round 3. Participants will be provided with feedback as in round 2 and invited

Chapter 2

to rate each outcome. All outcomes classified as ‘consensus in’ (Table 2.2) will be brought forward to the consensus meeting.

2.5.4 Step 3: Consensus Meeting

The final stage of this work will be an international consensus meeting with members of the relevant stakeholder groups to discuss, review and vote on a final COS. We plan to have at least 20 participants, with members from each stakeholder group participating to ensure maximum diversity of the demographic representation. Participants will be sent the results of round 3 of the Delphi at least 2 weeks prior to the meeting to allow time for reflection of their answers and those of others. This meeting will be chaired by an experienced, non-voting facilitator. After a prior discussion on each outcome, anonymous electronic voting will take place whereupon consensus will be defined as per previously stated in the eDelphi survey. Prior to the conclusion of the consensus, the recommended list of outcomes will be reviewed and finalised.

2.6 Dissemination and Implementation

Upon completion of the consensus meeting and agreement on the final COS, a manuscript will be prepared in compliance with the CO-STAP recommendations⁶⁹, published and disseminated. To encourage researchers and clinicians to use the COS, we aim to present this work at national and international conferences.

2.7 Conclusion

Currently, there is no published COS for RCTs evaluating the effectiveness of interventions in pregnant women with PGDM. The COS will enable greater comparison between and information synthesis across RCTs in the treatment of pregnant women with PGDM. In addition, this COS will help improve trial reporting and minimise research waste by prioritising the collection and reporting of outcomes that matter to all relevant stakeholder group.

Chapter 3

Chapter 3: The Systematic Review

3.1 Chapter Introduction

This chapter introduces paper 2: A systematic review on outcome reporting in randomised controlled trials assessing treatment interventions in pregnant women with PGDM. Outcomes extracted from the literature in this systematic review formed the basis of the eDelphi survey.

3.2 Paper 2: A Systematic Review on Outcome Reporting in Randomised Controlled Trials Assessing Treatment Interventions in Pregnant Women with Pregestational Diabetes

Kgosidialwa O, Bogdanet D, Egan A, Newman C, O'Shea PM, Biesty L, McDonagh C, O'Shea C, Devane D, Dunne F; INSPIRED group. A Systematic Review on Outcome Reporting in Randomised Controlled Trials Assessing Treatment Interventions in Pregnant Women with Pregestational Diabetes. BJOG. 2021. <https://doi.org/10.1111/1471-0528.16842>.

Chapter 3

3.3 Abstract

Background Pre-gestational diabetes mellitus (PGDM) is associated with adverse pregnancy outcomes. Studies assessing interventions to improve maternal and infant outcomes have increased exponentially over the last number of years. Several outcomes in this field of maternal diabetes are rare outcomes making it difficult to synthesise evidence.

Objectives To collect outcomes reported in studies assessing treatment interventions in pregnant women with PGDM.

Search Strategy CENTRAL, Web of Science, Medline, CINAHL, Embase and ClinicalTrials.gov from their inception until 27th January 2020.

Selection Criteria Any randomised controlled trial (RCT) assessing treatment interventions in pregnant women with PGDM reported in English.

Data Collection and Analysis Two independent reviewers assessed the suitability of articles and retrieved the data. Outcomes extracted from the literature were broadly categorised into maternal, fetal/ infant or other outcomes by the study advisory group (SAG).

Main results Sixty seven of the 1475 studies identified fulfilled the inclusion criteria. The median number of outcomes reported per study was 15 (range 1- 46). The majority of studies were from North America and Europe. Insulin and metformin were the most commonly investigated pharmacological interventions. Glucose monitoring was the most assessed technological intervention. One hundred and thirty-one unique outcomes were extracted; maternal (n=69), fetal/infant (n=61) and other (n=1).

Conclusions Outcome reporting in treatment interventions trials of pregnant women with PGDM is varied, making it difficult to synthesise evidence especially for rare outcomes. Systems are needed to standardise outcome reporting in future clinical trials and thus facilitate evidence synthesis in this area of maternal diabetes.

Registration The systematic review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration ID: CRD42020173549).

Chapter 3

3.4 Introduction

Diabetes mellitus is one of the most common pre-existing medical conditions complicating pregnancy⁹³. Women with pre-gestational diabetes mellitus (PGDM) and their babies are particularly vulnerable to adverse pregnancy outcomes compared to women with normal glucose tolerance. The St. Vincent declaration (1989), stating that pregnancy outcomes in women with diabetes should approximate that of women without diabetes, has not been achieved²⁸. PGDM is associated with increased morbidity to both mother and baby including preterm birth, small (SGA) and large for gestational age (LGA), macrosomia, congenital malformations and pre-eclampsia (PET)²⁹.

In recent years, there has been a significant increase in treatment interventions to help alleviate morbidity and mortality in pregnant women with PGDM. Some such interventions include education programmes^{94,95} pharmacological interventions^{96,97}, technological interventions^{82,98} and pre-pregnancy care (PPC)⁴⁴. In addition, organisations such as Diabetic Pregnancy Study Group (DPSG) and International Association of Diabetes in Pregnancy Study Groups (IADPSG), have facilitated and disseminated research to improve outcomes in these high-risk pregnancies. Guidelines for the management of pregnant women with PGDM are also easily available globally to help clinicians care for these women.

It is important to monitor over time whether these interventions have had a positive impact on morbidity and mortality in PGDM pregnancies. There is evidence to suggest that many of these interventions have yielded positive results^{49,51}. However, robust evidence on how different interventions affect morbidity and mortality in pregnancies complicated by PGDM is inconsistent, in part due to the measurement and reporting of a variety of outcomes^{65,99}. One way to overcome the problem of variable outcome reporting is through the creation of Core Outcome Sets (COSs) which measure a consensus-derived collection of outcomes to be reported on a particular healthcare topic. This work involves all relevant stakeholders including patients and patient representatives, healthcare workers, researchers and policymakers. The CoRe Outcomes in Women's health (CROWN) initiative, established to improve outcome reporting in maternal diabetes, made a call to researchers to produce, disseminate and implement COSs to improve outcome reporting, build evidence synthesis and reduce research waste¹⁰⁰. The initial step in the COS development process is a systematic review to create a list of all unique outcomes reported in the literature.

Chapter 3

The aim of this systematic review was to collate a list of outcomes reported in randomised controlled trials (RCTs) evaluating treatment interventions in pregnant women with PGDM. This systematic review formed the basis for an eDelphi process to create a COS in this topic.

3.5 Methods

The protocol for this systematic review has been published¹⁰¹. This systematic review is registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number CRD42020173549). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines^{102, 103}.

RCTs assessing any treatment interventions of pregnant women with PGDM were included in the study. Non-randomised controlled trials, longitudinal follow-up studies, secondary analysis, reviews, reports of conference proceedings or abstracts where there was no complete description of the trial methodology were excluded. Only studies reported in English were eligible for inclusion. Any comparator and any outcome were noted. Studies were restricted to interventions that occurred during pregnancy only.

The following databases were searched: CENTRAL (via the Cochrane Library), Web of Science (WOS), Medline (via OVID platform), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (via EBSCO host platform) and Embase. In addition, ClinicalTrials.gov was searched for ongoing trials and references of relevant articles were reviewed for studies not captured in the search. There was no time restriction, however, the final database search was completed on 27th January 2020.

A search strategy was formulated with the assistance of the school librarian at the National University of Ireland, Galway (NUI Galway). A combination of keywords and Medical Subject Headings (MeSh) terms was used to search for specific concepts. These were then combined using Boolean operators to formulate the final search strategy. A full search strategy is shown in Appendix 1.

Studies deemed suitable for inclusion were identified from the search using the predetermined inclusion criteria. The reference management tools Zotero (<https://www.zotero.org/>) and Rayyan (<https://www.rayyan.ai/>) were used to manage and identify duplicate articles downloaded from the search results. Two independent reviewers (OK and DB) screened titles

Chapter 3

and abstracts of the selected studies to ensure eligibility. Full-text papers of selected studies were reviewed by both reviewers prior to final decision regarding inclusion. Disagreements were resolved through discussion and recourse to a third author (FD) if necessary.

All reported outcomes were extracted from the ‘methods’ and ‘results’ section of each paper. A data extraction template consisting of the following parameters was used to extract outcomes; authors, journal and year of publication, the condition of interest (T1DM, T2DM or both), outcome of interest and time points or periods of outcome measurement. We also assessed how each outcome was defined and the instruments or indicators used to measure the outcome. Two independent reviewers (OK and DB) assessed the articles independently, reviewed outcomes together and ensured that all outcomes were identified and included.

Risk of bias in individual studies was not carried out as our study aimed to extract all outcomes reported in the literature regardless of reporting bias. In addition, some of the included studies were ongoing, making bias reporting not possible.

Outcomes extracted from the literature were broadly categorised into maternal, fetal/ infant or other outcomes. The study advisory group (SAG) including women with PGDM, healthcare providers and researchers then carefully reviewed the outcomes and 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. Where clarification was needed for particular outcomes regarding suitability for grouping, advice was sought from the relevant experts.

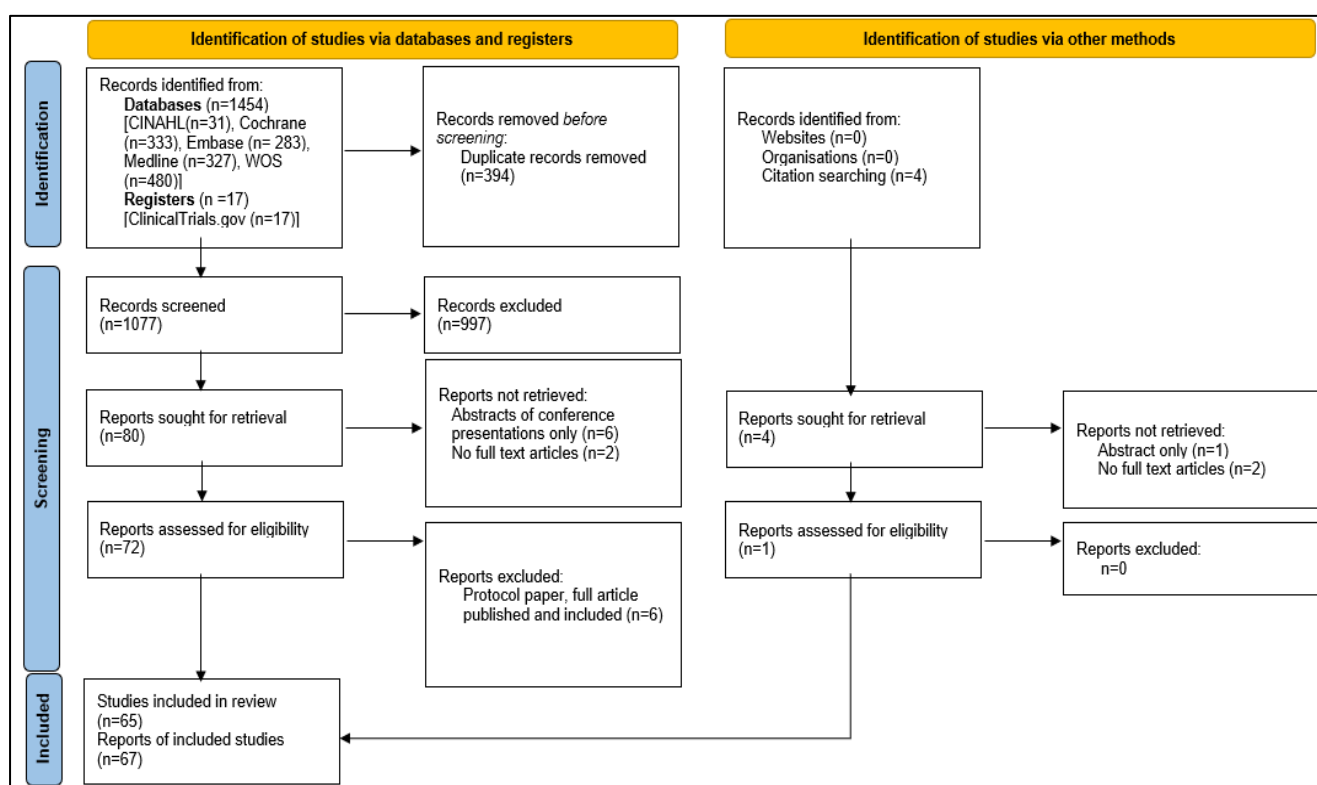
3.6 Results

Of the 1475 potentially relevant studies, 67 (48, 49, 53, 57-64, 79, 82, 94-98, 104-152) fulfilled the inclusion criteria as shown on the PRISMA flowchart¹⁰³ (figure 3.1). The number of outcomes reported in each study is shown in Table 3.1. The median number of maternal and fetal/infant outcomes reported per article were seven and eight respectively. On average, most studies reported a median of 15 outcomes. The number of overall reported outcomes ranged from one⁹⁵ to 46⁴⁹. Twenty-four, 10 and 14 studies assessed interventions in women with pre-existing type 1 diabetes (T1DM), type 2 diabetes (T2DM) and a combination of both respectively. In some cases, the population was defined as women with PGDM (n= 18) or insulin requiring diabetes (n=1).

Chapter 3

Studies were carried out in North America (n=33), Europe (n=30), Asia (n=10), South America (n=7), Africa (n=6) and Australia/ New Zealand (n=6). The earliest study was published in 1971¹³⁸ with the most recent studies still ongoing. Interventions are shown in Table 3.2. The most researched pharmacological interventions were insulin (n=14) and metformin (n=9). Glucose monitoring (n=12) was the most assessed technological intervention, with continuous glucose monitoring (CGM)(n=6) accounting for half of the studies.

Figure 3.1 PRISMA flowchart of selection of studies



Chapter 3

Table 3.1 Number of outcomes reported in each study

	Article	Number of Maternal Outcomes	Number of Fetal/ Infant Outcomes	Number of Other Outcomes	Total Number of Outcomes	Type of Diabetes
1	Ainuddin JA et al (2015)	9	15	3	27	T2DM
2	Bartal MF et al (2018) †	8	11	0	19	T2DM
3	Bartholomew ML et al (2015)	4	0	0	4	T2DM
4	Beazley D et al (2005)	2	3	0	5	Insulin requiring diabetes
5	Berry DC et al (2018) *	15	30	0	45	T2DM
6	Beyuo T et al (2015)	3	0	0	3	T2DM
7	Brooten D et al (2001)	7	8	3	18	PGDM
8	Burkart W et al (1988)	7	16	0	23	T1DM, T2DM
9	Caritis Set al (1998)	4	5	0	9	T1DM, T2DM
10	Carr KJE et al (2004)	4	1	0	5	T1DM
11	Cordua et al (2013)	6	10	0	16	T1DM
12	Demarini S et al (1994)	5	8	0	13	PGDM
13	Di Biase N et al (1997)	12	1	0	13	PGDM
14	Dieb AS et al (2019) †	7	7	0	14	T1DM
15	Feghali MN et al (2018) †	3	5	0	8	T1DM
16	Feig DS et al (2017)	26	20	0	46	T1DM
17	Feig DS et al (2016) *	11	14	0	25	T1DM
18	Finnegan C et al (2019) *	6	14	0	20	T1DM, T2DM
19	Forster DA et al (2017)	7	12	2	21	T1DM, T2DM
20	Garmy G et al (2017) †	6	8	0	21	PGDM
21	Gray L et al (2018) †	6	0	0	6	PGDM
22	Hanson U et al (1984)	10	9	0	19	PGDM
23	Hayden T et al (2012)	4	6	0	10	T1DM, T2DM
24	Herrera KM et al (2015)	8	5	0	13	T2DM
25	Hickman MA et al (2013)	11	15	0	26	T2DM
26	Hod M et al (2008) #	8	18	0	26	T1DM
27	Hod M et al (2014) #	7	12	0	19	T1DM
28	Horvaticek M et al (2017)	6	5	0	11	T1DM
29	Ibrahim MI et al (2014)	4	11	0	15	PGDM
30	Incerpi MH et al (2001)	3	6	0	9	PGDM
31	Jovanovic-Peterson L et al (1992)	5	15	0	20	T1DM, T2DM
32	Kjos SL et al (1993)	1	10	0	11	PGDM
33	Laatikainen L et al (1987)	5	0	0	5	T1DM
34	Lin L et al (2018) *	6	9	0	15	T1DM, T2DM
35	Linden K et al (2018)	6	3	0	9	T1DM
36	Manderson JG et al (2003)	11	22	0	33	T1DM
37	Mathiesen ER et al (2012) #	13	0	0	13	T1DM
38	Mathiesen ER et al (2007) #	17	3	0	20	T1DM
39	McCance DR et al (2010)	14	21	0	35	T1DM
40	Mimouni F et al (1987)	2	6	0	8	PGDM
41	Min Y et al (2014)	0	28	0	28	T2DM
42	Moninx WM et al (1997)	4	13	0	17	PGDM
43	Mostello D et al (2017) †	1	0	0	1	PGDM
44	Murphy HR et al (2008)	5	15	0	20	T1DM, T2DM
45	Murphy HR et al (2011)	10	0	0	10	T1DM
46	Nachum et al (1999)	9	15	0	24	PGDM
47	Ney D et al (1982)	7	5	0	12	T1DM, T2DM
48	Nor Azlin MI et al (2007)	8	2	0	10	PGDM
49	Notelovitz M (1971)	5	7	0	12	PGDM
50	Perichart-Perera O et al (2012)	7	11	0	18	T2DM
51	Persson B et al (2002)	10	13	0	23	T1DM
52	Petrovski G et al (2013)	7	3	0	10	T1DM
53	Polsky S et al. (2018) †	17	3	0	20	T1DM
54	Refuerzo JS et al (2015)	7	9	0	16	T2DM
55	Ringholm L et al (2018) †	13	10	0	23	T1DM, T2DM
56	Rosenberg VA et al (2006)	3	9	0	12	PGDM
57	Sacks DA et al (2006)	5	9	0	14	T1DM
58	Secher AL et al (2013)	11	10	0	21	T1DM, T2DM
59	Stewart ZA et al. (2018)	16	7	0	23	T1DM
60	Stewart ZA et al. (2016)	15	6	0	21	T1DM
61	Varner MW (1983)	4	7	0	13	PGDM
62	Voormolen DN et al (2018)	10	18	0	28	T1DM, T2DM
63	Wen SW et al (2018)	11	13	0	24	T1DM, T2DM
64	Wojcicki JM et al (2001)	6	1	0	7	T1DM
65	Wright TE et al (2000)	1	6	0	7	T1DM, T2DM
66	York R et al (1997)	5	6	1	12	PGDM
67	NoNovo Nordisk (2017) †	9	10	0	19	T1DM

T2DM Type 2 diabetes mellitus, T1DM Type 1 diabetes mellitus, PGDM Pregestational diabetes mellitus.

† Protocol from clinicaltrials.gov. *Published study protocol. #One study, two reports; Hod M et al (2008) and Mathiesen ER et al (2007), Hod M et al (2014) and Mathiesen ER et al (2012).

Chapter 3

Table 3.2 Types of interventions reported in each study

Intervention	Total number of studies
Pharmacology	
Insulin	14
Metformin	9
Aspirin	3
Vitamin C and Vitamin E	2
Eicosapentaenoic acid and docosahexaenoic acid	2
Sulphonylurea	1
Folic acid	1
Intravenous fluids	1
Technology	
Glucose monitoring	12
Closed-loop insulin delivery system	4
Messaging and education systems	3
Insulin pump	2
Other	
Glycaemic targets	3
Home care (versus hospital care)	2
Induction of labour	2
Diet	2
Insulin regimen	1
Early discharge (versus routine discharge)	1
Expressing milk in the antenatal period	1
Cognitive behavioural therapy	1

Forty-one (61.2%) studies specifically reported primary outcomes. Four studies (6.0%) reported the primary outcome as a composite outcome. There were differences in items reported in composites. For example, two of the studies assessing metformin treatment, one composite outcome included; perinatal mortality, preterm birth, neonatal hypoglycaemia, hyperbilirubinemia, LGA, SGA, low birth weight and birth trauma¹⁰⁵. The other study included the following in the composite outcome; preterm birth; birth injury; moderate/severe respiratory distress; neonatal hypoglycaemia; NICU admission and pregnancy loss⁵³. Thirty-six (53.7%) studies specifically reported secondary outcomes.

No studies specifically engaged Public and Patient Involvement (PPI). Wen et al ¹⁴⁹ commented that although they did not actively seek patient engagement, physicians' input was provided through a survey, suggesting that their patient population would be interested in the trial and their advice was sought on best practices to roll out the trial. However, no explicit PPI was sought.

Chapter 3

Data extracted from the first ten studies are shown in Table 3.3. Prior to SAG review, a total of 210 outcomes were extracted from the literature (Table 3.4). The SAG then reviewed the outcomes, combining similar outcomes, removing duplicates and clarifying outcome terminology. Some examples of outcomes that were combined are as follows; vaginal birth and caesarean section birth were combined to 'mode of birth', sepsis and pyelonephritis as 'maternal infection' and birthweight SD score, birthweight Z score, birthweight percentile, customised birthweight centiles as 'birthweight'. Some outcomes that were not clearly defined were not listed as a unique outcome. For example, pregnancy loss was listed as miscarriage, stillbirth, ectopic pregnancy or pregnancy termination.

Chapter 3

Table 3.3 Data extraction template

Author (Year of publication; Publication Journal)	Study Title	Population (N)	Intervention (N)	Comparator (N)	Outcomes	Gestation week	Number of outcomes	Country of study
Carr KJE et al. (2004; The Journal of Obstetrics and Gynaecology)	A Randomised Controlled Trial of Insulin Lispro Given Before or After Meals in Pregnant Women with Type 1 Diabetes-The Effect on Glycaemic Excursion	T1DM (N=9)	Insulin lispro immediately before a standardised meal (N=5)	Insulin lispro immediately after a standardised meal (N=9)	Maternal FBG; PPG (12 time points); glucose excursion. Fetal/Infant: Fetal compromise.	-	Maternal= 4; Fetal/infant= 1; Other= 0 Total= 5	United Kingdom
Curtis S et al. (1998; The New England Journal of Medicine)	Low-Dose Aspirin to Prevent Preeclampsia in Women at High Risk	T1DM, T2D, insulin treated diabetes, chronic HTN, multifetal gestations, prior PET (N=2539)	Aspirin 60 mg daily (N=1273)	Placebo daily (N=1266)	Maternal PET; abruption placenta; PPH; treatment compliance. Fetal/Infant: Preterm neonatal bleeding; perinatal death.	13 and 26 weeks	Maternal= 4; Fetal/infant= 5; Other= 0 Total= 9	USA
Burkert W et al. (1988; Gynecologic and Obstetric Investigation)	Complications and Fetal Outcome in Diabetic pregnancy. Intensified Conventional versus Insulin Pump Therapy	T1DM (N=117)	CSII (N=48)	Intensive conventional treatment (N=41) Conventional treatment (N=28)	Maternal Mode of delivery; premature labour; PPROM; PET; DKA; hypoglycaemia; pyelonephritis. Fetal/Infant: Gestational age; birth weight; birthweight >90 th centile; macrosomia; birth weight <10 th centile; IUGR; premature delivery; perinatal mortality; stillbirth; infant mortality; hypoglycaemia; congenital malformations; polyhydramniol; hyperbilirubinemia; hypocalcaemia; respiratory distress.	First trimester	Maternal= 7; Fetal/infant= 16; Other= 0 Total= 23	Germany
Brooken D et al. (2001; American Journal of Managed Care)	A Randomized Trial of Nurse-Specialist Home Care for Women with High-Risk Pregnancies: Outcomes and Costs	PGDM, GDM, chronic HTN, preterm labour/ labour (N=173)	Half of the prenatal care provided in women's homes by nurse specialists with master's degrees (N=85)	Usual treatment (N=88)	Maternal Prenatal hospitalisations; delivery hospitalisations; postpartum re-hospitalisations; prenatal acute care visits; postpartum acute care visits; maternal affect; satisfaction with care. Fetal/Infant: Gestational age at birth; birth weight; low birth weight; perinatal mortality; preterm birth; days hospitalised after delivery; days re-hospitalised; acute care visits.	First antenatal visit	Maternal= 7; Fetal/infant= 3 Total= 18	USA
Beyuo T et al. (2015; PLOS One)	Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnant Women with Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A	T2DM and GDM (N=87)	Metformin (N=47)	Insulin (N=40)	Maternal PRG; PPG; maternal weight gain.	20 to 30	Maternal= 3; Fetal/infant= 0; Other= 0 Total= 3	Ghana
Berry DC et al. (2018; BMC Pregnancy and Childbirth)	Rationale, Design and Methods for the Medical Optimization and Management of Pregnancies with Overt Type 2 Diabetes (MOMPOD) study	T2DM (N=1200)	Metformin and insulin	Insulin	Maternal FBG; PPG; compliance; side effects of treatment; gestational weight gain; hypoglycaemia; death; adverse events; DKA; ICU admission; intubation; renal failure; placental, abruption; PET, miscarriage. Fetal/Infant: Birth, fat mass; length; head circumference; perinatal mortality; neonatal death; stillbirth; IVH; NEC; trauma; fracture; preterm delivery; hypoglycaemia; polyhydramniol; LGA; SGA; hyperbilirubinemia; NICU; intubation; intestinal perforation; respiratory problems; seizure; hypotension; cardiac arrhythmias; QTc prolongation; conjunctivitis; wound infection; ROP; postpartum feeding experience; hearing impairment.	10 to 20+6	Maternal= 15; Fetal/infant= 30; Other= 0 Total= 45	USA
Beazley D et al. (2015; American Journal of Obstetrics and Gynecology)	Vitamin C and E Supplementation in Women at High Risk for Preeclampsia: A Double-blind, Placebo-Controlled Trial	History of prior PET, chronic HTN, insulin-requiring DM, or multiple	Vitamin C and vitamin E (N=52)	Placebo (N=48)	Maternal PET; pregnancy loss before 20 weeks' gestation. Fetal/Infant: Delivery week; birth weight; premature birth.	14 to 20	Maternal= 2; Fetal/infant= 3; Other= 0 Total= 5	USA
Bartolomew ML et al. (2015; Clinical Diabetes)	Managing Diabetes in Pregnancy Using Cell Phone/Internet Technology	T2DM or GDM (N=74)	Cell phone-internet home glucose reporting system (N=40)	Voice mail home blood glucose reporting first (N=34)	Maternal FBG; PPG; compliance with SMBG reporting; satisfaction with intervention.	<30+1	Maternal= 4; Fetal/infant= 0; Other= 0 Total= 4	USA
Bartol MF et al. (2018; Clinical Trials.gov research)	Detemir Versus NPH for Type 2 Diabetes Mellitus in Pregnancy: A Comparative-effectiveness Open Label, Randomized Controlled Trial	T2DM (N=108)	Insulin detemir	Neutral Protamine Hagedorn insulin (NPH) (N=100)	Maternal FBG; PPG; hypoglycaemia, PET; gestational hypertension; vaginal delivery; caesarean section delivery; treatment compliance; daily insulin dose; daily metformin dose; total weight gain in pregnancy. Fetal/Infant: Gestational age at delivery; NICU admission; NICU length of stay; neonatal hypoglycaemia; RDS; shoulder dystocia; LGA; macrosomia; SGA; 5-minute APGAR score \leq 5; jaundice requiring therapy.	\leq 20	Maternal= 8; Fetal/infant= 11; Other= 0 Total= 19	USA
Anuddin JA et al. (2015; Journal of diabetes research)	Metformin Treatment in Type 2 Diabetes in Pregnancy: An Active Controlled, Parallel-Group, Randomized, Open Label Study in Patients with Type 2 Diabetes in Pregnancy	T2DM (N=206)	Metformin (N=106)	Insulin (N=100)	Maternal Glycemic control; FHT; PET; gestational hypertension; delivery; vaginal delivery; treatment compliance; daily insulin dose; daily metformin dose; total weight gain in pregnancy. Fetal/Infant: Gestational age at delivery; birth weight; NICU admissions; neonatal hypoglycaemia; LGA; macrosomia; SGA; TTN; RDS; pneumonia; sepsis; jaundice; birth trauma; alive baby; BGL at birth; APGAR score 5 mins. Other: Cost of pregnancy; insulin cost; metformin cost.	\geq 4	Maternal= 9; Fetal/infant= 15; Other= 3 Total= 27	Pakistan

Chapter 3

T2DM Type 2 diabetes mellitus, T1DM Type 1 diabetes mellitus, PIH Pregnancy induced hypertension, PET Pre-eclampsia, 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, BGL Blood glucose levels, BP Blood pressure, IV Intravenous, FBG Fasting plasma glucose, PPG Post prandial glucose, GDM Gestational diabetes mellitus, SMBG Self-monitoring of blood glucose, HTN Hypertension, DM Diabetes mellitus, DKA Diabetic ketoacidosis, ICU Intensive care unit, IVH Intraventricular haemorrhage, NEC Necrotising enterocolitis, ROP Retinopathy of prematurity, PGDM Pregestational diabetes mellitus, CSII Continuous subcutaneous insulin infusion, PPROM Preterm premature rupture of membranes; IUGR Intrauterine growth restriction; PPH Post-partum haemorrhage, HELLP Haemolysis elevated liver enzymes and low platelets.

Table 3.4 All outcomes extracted from the literature (N=210)

MATERNAL OUTCOMES				
	Complications	Blood/urine parameters and monitoring	Life impact/ psychological	Miscellaneous
1	Death	Fasting glucose	Satisfaction with intervention	Trimester specific daily insulin dose
2	Adverse events	Trimester specific fasting glucose	Improvement in fear of hypoglycaemia	Hourly insulin infusion rate
3	Skin reactions	Pre-prandial glucose	Fear of hypoglycaemia	Insulin dose during labour
4	Pregnancy induced (gestational) hypertension	Trimester specific pre-prandial glucose	Improved self-efficacy of diabetes management	Insulin treated during labour
5	Pre-eclampsia	Post prandial glucose	Diabetes distress	Insulin dose at time of birth of the baby
6	Severe PET	Trimester specific post prandial glucose	Health related quality of life	Daily metformin dose
7	Eclampsia	Self-monitored blood glucose	Improvement in maternal affect	Compliance with intervention
8	HELLP syndrome	Blood glucose	Views and experiences of women	Compliance with glucose testing
9	Proteinuria	Self-measured 8-point plasma glucose profile	Successful breastfeeding	Weight gain in pregnancy
10	Worsening chronic hypertension	Maternal blood glucose levels following first three milk expressing episodes	Return to normal activities	Change in body weight
11	Hypertensive disorders of pregnancy	Glycemic control		Excessive weight gain in pregnancy
12	Caesarean section delivery	Time to achieve glycaemic control		Duration of hospitalisation
13	Hypoglycaemia	Percentage of target glucose levels		Number/duration of antenatal hospitalisations
14	Mild hypoglycaemia	Time within range		Post-partum hospitalisations
15	Moderate hypoglycaemia	Percentage of high blood glucose levels		Unscheduled health care visits
16	Severe hypoglycaemia	Time above glycaemic target		Onset of labour (Spontaneous, induction or C-section)
17	Nocturnal hypoglycaemia	High blood glucose index		Hypoglycaemia awareness
18	Pregnancy loss	Percentage of low blood glucose levels		
19	Miscarriage	Time below glycaemic target		
20	Late spontaneous abortion	Duration of hypoglycaemia		
21	Ectopic pregnancy	Low blood glucose index		
22	Pregnancy termination	Glucose excursion		
23	Side effects of treatment	Glucose variability		
24	Diabetic ketoacidosis	Trimester specific HbA1c		
25	Progression of retinopathy	HbA1c, change from baseline to last measured or as stated		
26	ICU admission	HbA1c, at the time of the birth of the baby		
27	Intubation	Trimesters specific fructosamine		
28	Pulmonary embolus	Fructosamine change from baseline to last measured or as stated		
29	Pulmonary oedema	Fructosamine level, at the time of the birth of the baby		
30	Renal failure	Trimester specific C-peptide		
31	Placental abruption	Homeostatic model assessment- Insulin resistance		
32	Placenta praevia	Placental and endothelial function		
33	Antepartum haemorrhage	Plasma insulin levels		
34	Post-partum haemorrhage	Urinary glucose		
35	Haemorrhage			
36	Polyhydramnios			
37	Preterm labour			
38	Preterm rupture of membranes			
39	Prolonged labour			
40	Induction of labour			
41	Complications of labour induction			
42	Pyelonephritis			
43	Sepsis			

FETAL/ NEONATAL OUTCOMES				
	Complications	Biometrics and anthropometrics	Laboratory measures	Miscellaneous
1	Perinatal mortality	Birth weight	Blood glucose at birth	Alive baby
2	Neonatal morbidity	Birthweight SD score	Plasma glucose	Appropriate for gestational age
3	Resuscitation in the delivery room	Birthweight Z core	Cord glucose	Mode of delivery
4	Stillbirth	Infant weight	Cord pH	APGAR 1 min
5	Intrauterine fetal death	Birthweight percentile	Cord C peptide	APGAR score 5 mins
6	Neonatal death	Customised birthweight centiles	Cord insulin	APGAR score

Chapter 3

7	Infant mortality	Fetal weight gain	Cord IGF-1	Infant psychomotor development
8	NICU admission	Neonatal fat mass	Insulin antibodies	Postpartum feeding experience
9	NICU length of stay	Fetal fat mass		Infants receiving exclusive breast milk
10	Respiratory problems	Fetal lean mass		Duration of hospital stay
11	Transient tachypnoea of the newborn	Fetal long bone measurements		Frequencies of re-hospitalisations and acute care visits
12	Respiratory distress syndrome	Abdominal circumference		Admission rates
13	Perinatal asphyxia (apnoea)	Mid arm circumference		Neonatal neurological optimality score
14	Bronchopulmonary dysplasia	Neonatal body composition		
15	Chronic lung disease	Weight at 6 months		
16	Hypoxic ischaemic encephalopathy	Head circumference		
17	Periventricular leukomalacia	Birth head circumference SD score		
18	Assisted ventilation	Length		
19	Need for oxygen	Birth length SD score		
20	Fetal compromise	Shoulder circumference		
21	Neonatal hypoglycaemia	Gestational age at birth		
22	Severe neonatal hypoglycaemia (treated)			
23	Shoulder dystocia			
24	Birth trauma			
25	Fracture			
26	Large for gestational age			
27	Extremely LGA			
28	Macrosomia			
29	Small for gestational age			
30	Intrauterine growth retardation			
31	Low birth weight			
32	Malnutrition			
33	Premature birth			
34	Sepsis			
35	Infection			
36	Wound infection			
37	Conjunctivitis			
38	Jaundice			
39	Hyperbilirubinemia			
40	Phototherapy			
41	Polycythemia			
42	Erythrocytosis			
43	Hypocalcaemia			
44	Seizures			
45	Intraventricular haemorrhage			
46	Neonatal bleeding			
47	Necrotising enterocolitis			
48	Intestinal perforation			
49	Hypotension			
50	Cardiac arrhythmia			
51	QTc prolongation			
52	Retinopathy of prematurity			
53	Hearing impairment			
54	Congenital malformations			
55	Feeding problems			
OTHER OUTCOMES				
1	Cost of pregnancy			
2	Cost of the intervention			
3	Cost of care			
4	Insulin cost			
5	Metformin cost			
6	Cost effectiveness			

PET Pre-eclampsia, HELLP Haemolysis elevated liver enzymes and low platelets, ICU Intensive care unit, HbA1c Glycated haemoglobin, NICU Neonatal intensive care units, LGA Large for gestational age, SD Standard deviation, IGF-1 Insulin growth factor 1.

Differences in outcome definitions and time point measurements were noted. Definitions were not specified for all outcomes. We used the most reported maternal and neonatal complications as examples, PET and neonatal hypoglycaemia respectively (Table 3.5). Some but not all studies assessing PET as an outcome 1) specified the blood pressure (BP) measurement used for diagnosis 2) included HELLP syndrome, pulmonary oedema or other organ failure in the definition 3) specified the time point of 20 weeks gestation in the definition. There was significant variability in how neonatal hypoglycaemia was defined as shown in table 2. There

Chapter 3

was a total of 17 definitions given for neonatal hypoglycaemia. Time points for measuring neonatal hypoglycaemia ranged from ‘first glucose after birth’, ‘within 24 hours and/or 48 hours of birth’ to ‘thereafter’. For the most part, we did not consider the same outcome measured at different time points as unique outcomes but rather grouped them. Some definitions of neonatal hypoglycaemia included need for treatment while others did not.

On completion of outcome review, the SAG identified 131 unique outcomes (69 maternal, 61 fetal/infant and one other) for presentation to the first eDelphi round of COS development. Extracted outcomes listed according to frequency of reporting across all studies are shown in figure 3.2. The most commonly reported maternal outcomes ($n \geq 20$) across all studies were; pre-eclampsia ($n=30$), maternal hypoglycaemia ($n=28$), trimester specific HbA1c ($n=22$), self-monitored blood glucose ($n=22$), trimester specific insulin dose ($n=20$) and weight gain during pregnancy ($n=20$). The most commonly reported fetal/infant outcomes were; birthweight ($n=41$), gestational age at birth ($n=37$), mode of birth ($n=35$), neonatal hypoglycaemia ($n=34$), NICU admission ($n=27$), LGA ($n= 24$), congenital malformations ($n=24$), SGA) ($n=22$) and macrosomia ($n=20$).

Chapter 3

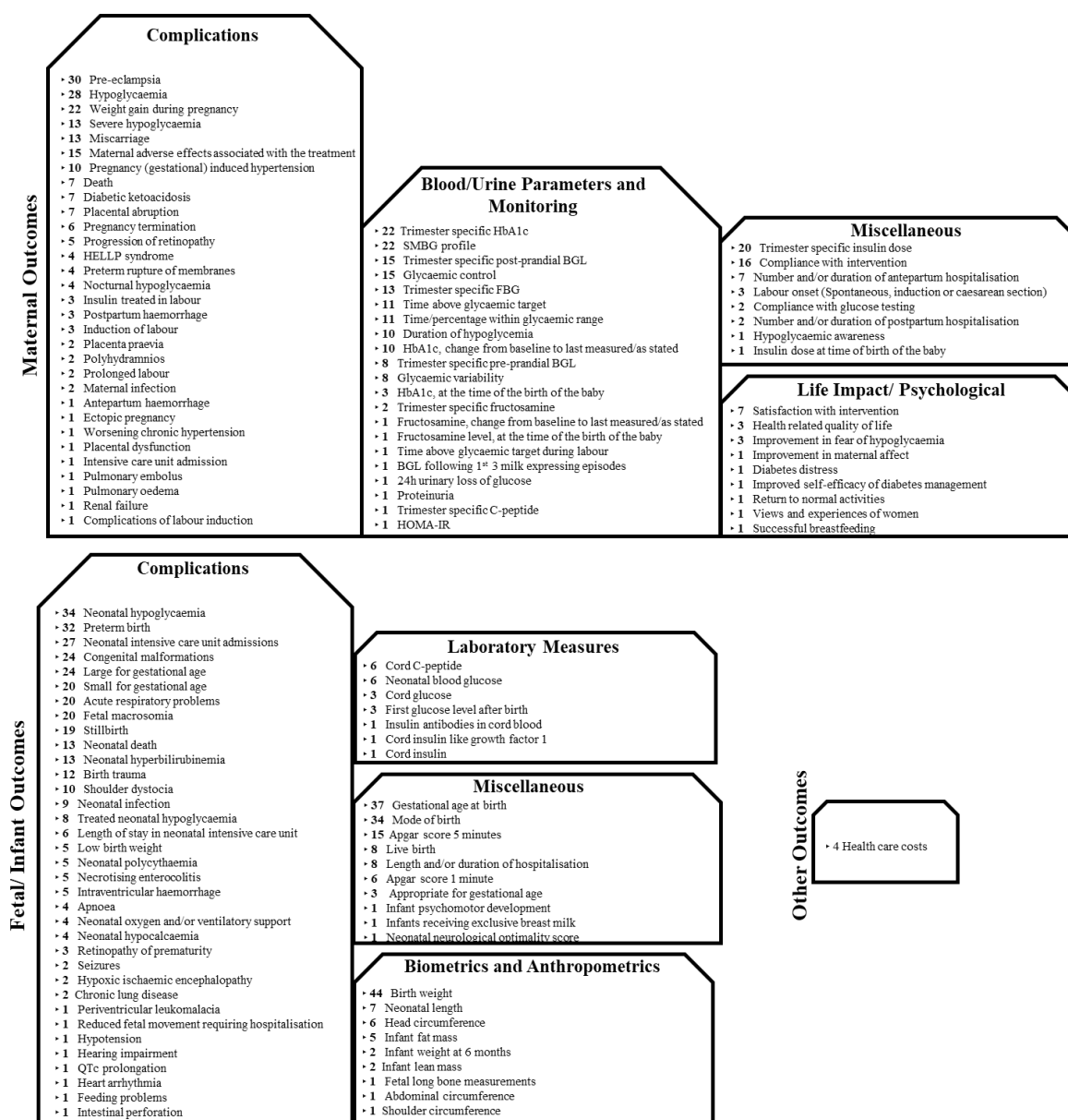
Table 3.5 Definitions and timepoints of the most reported maternal and fetal/neonatal complication

Outcome	Number of studies reporting outcome N (%)	Definitions and time points	Number of studies reporting similar outcome definition and timepoint N (%)		
Maternal					
PET	30 (44.8)	BP \geq 140/90 mmHg and proteinuria. ^{118,146}	2 (6.7)		
		BP >140/90 mmHg and proteinuria (\geq 300mg/24h). ¹³⁹	1 (3.3)		
		BP \geq 140/90 mmHg on two occasions with significant proteinuria. ⁹⁶	1 (3.3)		
		BP \geq 140/90 on two occasions at least 4h apart with significant proteinuria (\geq 300mg/24h) developing after 20 weeks of gestation. ^{63, 108,127,130,148}	5 (16.7)		
		DBP \geq 90 mmHg on 2 occasions \geq 4h apart and proteinuria (>2+ on dipstick, or urinary protein \geq 300 mg/24h, or PCR \geq 30 mg/mmol) in women \geq 20 weeks of gestation or diagnosis of HELLP syndrome. ¹⁴⁹	1 (3.3)		
		Development of HTN (BP \geq 140/90 mmHg on two occasions at least 4h apart) plus one of: proteinuria (\geq 300mg/24h or 2 dipstick-test \geq 2+/ 100mg/dl), thrombocytopenia (platelet <100,000/mm ³) or pulmonary oedema. ⁶²	1 (3.3)		
		New-onset HTN from gestational week 20 to delivery and simultaneous proteinuria or presence of eclampsia, HELLP syndrome, or other severe organ involvement. ⁶⁰	1(3.3)		
		No specific definition. ^{49,104,64,105, .53,114,119,58,59,129,52,138,140,142,143,61,79,48}	18 (60.0)		
		Fetal/ infant			
		Neonatal hypoglycaemia	34 (50.7)	BGL <2.6 mmol/L (47mg/dl). ¹⁴⁸	1 (2.9)
BGL <2.5 mmol/l (45 mg/dl). ¹¹²	1 (2.9)				
Two-hour plasma glucose < 2.5 mmol/l (45mg/dl). ^{109,146}	2 (5.9)				
BGL <2.2mmol/l (40mg/dl). ^{57,120}	1 (2.9)				
BGL<1.9mmol/l (35 mg/dL) within the first 24 hours of life. ^{145,144}	2 (5.9)				
BGL <1.9 mmol/l (35mg/dl) in term infants or <1.4 mmol/l (25mg/dL) in preterm infants at least on two different occasions during first 48 hours of life. ¹³⁵	1 (2.9)				
Blood glucose < 1. 7 mmol/L (31mg/dl). ^{118,127,147}	3 (8.8)				
BGL of < 2.6 mmol/L (47mg/dl), measured before feeds. ¹¹⁵	1 (2.9)				
CBG <1.7 mmol/l (30mg/dl) on two or more occasions in the first 48 h of life. ¹⁴¹	1 (2.9)				
BGL <1.7 mmol/l (30 mg/dl) in the first 24 hours of life and <2.2mmol/l (40 mg/dl) thereafter. ¹⁵¹	1 (2.9)				
BGL \leq 1.7 mmol/L (31 mg/dL) or \leq 2.5mmol/L (45 mg/dl) within the first 24 hours after birth. ⁶⁰	1 (2.9)				
BGL \leq 1.7 mmol/L (30 mg/dL) during the first 24 h after birth or a BGL \leq 2.5 mmol/L (45 mg/dL) between 24 and 48 hours after birth. ⁵⁹	1 (2.9)				
Hypoglycaemia requiring dextrose treatment. ^{49, 143,79,48}	4 (11.8)				
BGL < 2.2mmol/l (40 mg/dL) in the first 24h of life and < 2.8mmol/l (50 mg/dL) after or requiring medical therapy. ¹⁰⁴	1 (2.9)				
CBG < 2.2mmol/l (40mg/dl) or any hypoglycaemia that requires IV fluid treatment. ¹⁰⁵	1 (2.9)				
BGL < 2.6 mmol/l (47mg/dl) and requiring treatment. ⁵⁸	1 (2.9)				
Hypoglycaemia requiring intravenous dextrose therapy with BGL <1.4mmol/l (25mg/dL) ⁹⁶	1 (2.9)				
No specific definition. ^{108,53,116,122,125,134,138,142,61}	9 (26.4)				

BP Blood pressure, DBP Diastolic blood pressure, PCR Protein creatinine ratio, HELLP Haemolysis, elevated liver enzymes, low platelets, HTN Hypertension, BGL Blood glucose levels, CBG Capillary blood glucose, PG Plasma glucose.

Chapter 3

Figure 3.2 Reported outcomes listed according to frequency of reporting (n=67)



HbA1c Glycated haemoglobin, HELLP Haemolysis, elevated liver enzymes and low platelets, SMBG Self-monitored blood glucose, BGL Blood glucose levels, FBG Fasting blood glucose, HOMA-IR Homeostatic model assessment- Insulin resistance.

Fifteen (22.4%) studies involved patients in middle to low-income countries (LMIC). Of these, six studies included collaborations between high income countries (HIC) and LMIC. Interventions used in LMIC were insulin (n=6), metformin (n=4), sulphonylurea (n=1), diet (n=1), aspirin (n=1), folic acid (n=1) and glucose monitoring (n=1). The most reported maternal outcomes in studies involving LMIC were PET (n=7), glucose control (n=7) and adverse events

Chapter 3

(n=7). The most reported fetal/infant outcomes in LMIC studies were stillbirth (n=10), preterm birth (n=10), neonatal hypoglycaemia (n=10) and birthweight (n=8).

There were differences in the outcomes reported for each intervention. To underscore this point, we assessed the three commonly reported outcomes (maternal and fetal/infant) for the most researched intervention: insulin. Overall, there were 14 published articles from 12 studies assessing insulin in pregnancy. With the exception of only two studies^{116, 145}, most of the studies were performed in the first or second trimester. Of these, PET was reported in seven studies, maternal hypoglycaemia was reported in 11 studies, with only five studies reporting on severe hypoglycaemia. Only four studies reported on trimester specific HbA1c. Neonatal birthweight was reported in eight trials. In one study¹⁴⁵, the intervention was during labour and thus would not have been expected to have any effect on birthweight. Six studies reported gestational age at birth. Neonatal hypoglycaemia was reported in eight studies.

3.7 Discussion

Main Findings

We identified significant heterogeneity in outcome reporting and a need to develop a COS in studies assessing treatment interventions in pregnant women with PGDM. The differences are both in ‘what’ outcomes to report and ‘how’ to report these outcomes. The IADPSG has formulated a repository of definitions for outcomes commonly reported in the literature in order to help standardise the ‘how’ to report these outcomes⁶⁵. One of the common inconsistencies in outcome reporting found in this study was the variations in time points at which each outcome was measured. This is not unique to this study¹⁵³. In addition, there were variations in some outcome definitions according to national guidelines.

Strengths and Limitations

There are some limitations to this study. One limitation is that there is no consensus on how outcomes extracted from the literature should be classified. The Core Outcome Measures in Effectiveness Trials (COMET), an initiative that aims to bring together people interested in the development and application of COSs has endorsed the use of a 38-item scale to classify individual outcomes¹⁵⁴. Because our study involved two populations (mother and baby), we found this taxonomy unsuitable.

Chapter 3

Another limitation is that studies from LMIC were under represented. Therefore, it is not clear whether outcomes extracted from the current literature, mostly represented by HIC, would be clinically meaningful to these LMIC. PET was the most reported maternal outcome in both LMIC and HIC. However, unlike in HIC, preterm birth and stillbirth were the most reported outcomes in LMIC.

In our study, a large number of outcomes were extracted (n=210). As this systematic review was done in the context of a larger COS development study, it is important to recognise the risk of participant fatigue in the subsequent step (i.e., eDelphi survey) when such a large list of outcomes is generated. One way around this is grouping outcomes. There is currently no consensus on a reproducible method for developing a long list of unique outcomes for a COS with significant variation on how researchers extract, group, and count trial outcomes¹⁵⁵. We maintained a systematic approach to outcome extraction and grouping.

Interpretation

In recent years, standardisation of outcome reporting in the area of diabetes in pregnancy in order to reduce research waste and synthesise evidence has been recognised. This systematic review employed rigorous methodology to capture all outcomes reported in the literature in this important topic of maternal diabetes. We also identified significant heterogeneity in both the outcomes reported and how they are defined and measured.

Across all studies, outcomes in the maternal life impact/ psychological effects domain were the least reported. This is even more so for studies based in LMIC. Only one outcome ‘patient satisfaction’ was reported in this domain in studies carried out in LMIC. Integration of patient reported outcomes (PROs) into studies assessing interventions in pregnant women with PGDM may be one way of improving outcome reporting in this domain. Another way of improving outcome reporting in this domain might be engaging with PPI. One such initiative is the James Lind Alliance (JLA). The JLA through the Diabetes and Pregnancy Priority Setting Partnership (PSP) aims to improve research quality by ensuring that researchers and funders are aware of the issues that matter most to women with diabetes in pregnancy¹⁵⁶. We invited patients to participate as part of the SAG to ensure that their views and unique experiences are considered from study conception. Patients were actively involved in outcome review and finalising the list of unique outcomes. We hope that by involving women with diabetes in future studies, this will translate into an increase in outcomes in the life impact and psychological effects domain.

Chapter 3

The JLA 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 impact¹⁵⁶. Some of these questions include interventions in pregnant women with PGDM. This systematic review helps to inform what outcomes are reported in existing research in evaluating the effectiveness of interventions in pregnant women with PGDM. The planned COS derived from this work will help to prioritise a list of outcomes that are important to stakeholders including women with PGDM in this area of maternal diabetes.

PPC has been shown to improve some pregnancy outcomes⁴². Studies assessing PPC as an intervention were excluded from this review as a complimentary COS for studies evaluating the effectiveness of PPC for women with PGDM has already been developed⁸⁵. The planned COS will complement this prior work and provide stakeholders with guidance on outcome selection and reporting for studies conducted both before and during pregnancy in women with PGDM.

3.8 Conclusions

Outcome reporting in clinical trials evaluating treatment interventions in pregnant women with PGDM is varied both in ‘how’ and ‘what’ outcomes are measured and reported. A COS is needed to define what outcomes to report in future trials in this area of maternal diabetes. There is a need to prioritise and encourage LMIC participation and PPI in future studies evaluating treatment interventions in pregnant women to make research more applicable and impactful.

Chapter 4

Chapter 4: The Final Core Outcome Set

4.1 Chapter Introduction

This chapter introduces paper 3: A core outcome set for the treatment of pregnant women with pregestational diabetes: an international consensus study. Outcomes extracted from the literature in the systematic review were presented in a three round eDelphi survey to stakeholders to rank for inclusion into the final COS. Outcomes satisfying the inclusion criteria were then brought forward to a consensus meeting where key stakeholders voted on the final COS.

4.2 Paper 3: A Core Outcome Set for The Treatment of Pregnant Women with Pregestational Diabetes: An International Consensus Study

Kgosidialwa O, Bogdanet D, Egan A, Newman C, O'Shea PM, Griffin TP, McDonagh C, O'Shea C, Carmody L, Cooray SD, Anastasiou E, Wender-Ozegowska E, Clarkson C, Spadola A, Alvarado F, Noctor E, Dempsey G, Napoli A, Crowther C, Galjaard S, Loeken MR, Maresh MJA, Gillespie P, de Valk H, Agostini A, Biesty L, Devane D, Dunne F; INSPIRED group. A Core Outcome Set for The Treatment of Pregnant Women with Pregestational Diabetes: An International Consensus Study. BJOG. 2021. <https://doi.org/10.1111/1471-0528.16825>.

Chapter 4

4.3 Abstract

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.

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 round 2 and 3 respectively. Participants at the consensus meeting chose 19 outcomes for inclusion into the COS; trimester specific HbA1c, maternal weight gain during pregnancy, severe maternal hypoglycaemia, diabetic ketoacidosis, miscarriage, pregnancy induced hypertension, pre-eclampsia, maternal death, birth weight, 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.

Chapter 4

4.4 Introduction

Pre-gestational diabetes (PGDM) is defined as diabetes existing before pregnancy (including type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)). PGDM affects 1-4% of pregnancies depending on the background population^{15, 16}. PGDM prevalence continues to rise globally^{73, 157, 158}, partly due to the obesity epidemic and increasing maternal age¹⁵⁸. In the perinatal period, PGDM is associated with adverse pregnancy outcomes including congenital malformations¹⁵⁹, macrosomia¹⁶, preterm birth^{16, 160} and increased rates of caesarean delivery^{16, 160}. It is also associated with worsening diabetes complications such as diabetic retinopathy and nephropathy^{33, 161, 162}, at least during pregnancy, and developing co-morbidities such as pre-eclampsia (PET) and other hypertensive disorders^{76, 163}. Thus, PGDM poses a significant healthcare and economic burden. As a result, there have been advancements in education^{164, 165}, technology^{78, 79} and pharmacology⁵⁹ 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 pregnancy⁸³. However, there is no standardised approach to choosing which outcomes are measured or reported. This makes it difficult to compare and contrast the effects of various interventions and robustly synthesise evidence from a combination of trials⁶⁵. To help standardise reporting of outcomes in maternal diabetes, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) compiled and created a repository of definitions for maternal and fetal outcomes to be used universally⁶⁵. This work provides details on ‘how’ to collect but not ‘what’ outcomes to measure and report. While 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 care⁶⁶. 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.

Chapter 4

4.5 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 Core Outcome Measures in Effectiveness Trials (COMET) Initiative 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 (Registration ID: CRD42020173549). A detailed study protocol prepared in line with the Core Outcome Set-STANDARDISED Protocol Items (COS-STAP) Statement recommendations⁶⁹ has been published elsewhere¹⁰¹.

This study consisted of three work packages:

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.

4.5.1 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 (WOS), Medline (via OVID platform), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (via EBSCO host platform) and Embase. In addition, 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. The full search strategy is shown in Appendix 1.

Study Selection

The inclusion criterion for the study was 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

Chapter 4

necessary. Full-text papers of selected studies were reviewed by both reviewers before the final decision regarding inclusion.

Data Extraction

All reported outcomes were then extracted from the ‘methods’ and ‘results’ section of the paper. A sample of the extraction template is shown in Table 3.3.

Data Synthesis and Analysis

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

4.5.2 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 with PGDM and their representatives, healthcare professionals, researchers and policymakers. Women with PGDM were recruited via email, face to face and social media. We recruited healthcare professionals, researchers and policymakers with experience in the care of women with PGDM via email and social media and international organisations. The leads of national and international organisations involved in the care of women with PGDM were contacted via 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.

Chapter 4

Online international eDelphi surveys

In the email invite explaining the study, we provided a link to direct the stakeholders to the survey page. Participants were then able to provide explicit consent to take part in the study before proceeding. All participants who consented to the study were then 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 9-point Likert scale with a score of 1 representing an outcome of least importance and a score of 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 with PGDM 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 four weeks with reminder emails sent to those who had not completed the questionnaire within the first two 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 $\geq 70\%$ participants scoring 7 to 9 and $< 15\%$ scoring 1 to 3. 'Consensus out' was defined as $\leq 50\%$ 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 round 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.

Chapter 4

4.5.3 Consensus Meeting

A global virtual consensus meeting was carried out on the 1st of October 2020 via Zoom (<https://zoom.us/>) to finalise the COS. The meeting was chaired by an experienced, non-voting facilitator (DD). In his role, 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 $\geq 70\%$ 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.

4.5.4 Patient Involvement

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

4.6 Results

4.6.1 Systematic Review

The results of the systematic review are shown in Figure 3.1. Of the 1475 potentially relevant studies, 67 fulfilled the inclusion criteria. Two hundred and ten outcomes were extracted from the studies. Following SAG review where similar outcomes were combined, duplicate outcomes removed and outcome terminology clarified, 131 unique outcomes (69 maternal, 61 fetal/infant and one other) were presented for the first round (Table 4.1).

Chapter 4

Table 4.1 Outcomes included in eDelphi round 1 and percentage of participants scoring each outcome 7-9

	Outcome	Stakeholder Group			Total N=205
		Healthcare Workers N=123	Researchers & Policymakers N=36	Women with PGDM & their Representatives N=46	
Maternal blood/urine parameters and monitoring					
1.	Trimester specific fasting blood glucose	77.2%	69.2%	95.5%	80.8%
2.	Trimester specific pre-prandial blood glucose	67.0%	69.3%	91.2%	72.4%
3.	Trimester specific post-prandial blood glucose	75.8%	46.2%	88.9%	72.9%
4.	Duration of hypoglycemia	77.2%	77.0%	82.3%	78.4%
5.	Trimester specific C-peptide	19.3%	15.4%	64.5%	29.1%
6.	Time above glycaemic target	85.5%	77%	97.8%	87.7%
7.	Time above glycaemic target during labour	49.0%	56.2%	71.2%	53.8%
8.	24 hr urinary loss of glucose	13.0%	53.9%	32.7%	32.0%
9.	Glycaemic control	82.4%	61.6%	95.6%	87.2%
10.	Homeostatic model assessment- Insulin resistance (HOMA-IR)	30.4%	77.0%	80.0%	44.3%
11.	Self-measured 8-point plasma glucose profile	63.6%	53.9%	78.2%	66.4%
12.	Trimester specific HbA1c	76.7%	77.0%	93.4%	80.6%
13.	HbA1c, change from baseline to last measured or as stated	60.3%	69.3%	91.3%	67.8%
14.	HbA1c, at the time of the birth of the baby	54.8%	77.0%	71.7%	60.0%
15.	Maternal blood glucose levels following first three milk expressing episodes	30.2%	53.9%	69.6%	40.5%
16.	Trimester specific fructosamine	26.6%	61.6%	78.2%	40.5%
17.	Fructosamine, change from baseline to last measured or as stated	23.9%	46.2%	73.9%	36.6%
18.	Fructosamine level, at the time of the birth of the baby	20.5%	30.8%	67.4%	31.7%
19.	Time in range (TIR)	76.7%	84.7%	89.0%	80.0%
20.	Glycaemic variability	70.5%	77%	86.9%	74.6%
21.	Proteinuria	86.9%	84.6%	93.5%	88.2%
Maternal complications					
22.	Ectopic pregnancy	47.9%	53.9%	67.4%	52.7%
23.	Miscariage	84.9%	84.6%	78.3%	83.4%
24.	Pregnancy termination	65.7%	76.9%	47.8%	62.4%

Chapter 4

25.	Maternal hypoglycaemia	85.0%	84.6%	82.6%	84.4%
26.	Severe hypoglycaemic events	95.9%	92.3%	93.5%	95.0%
27.	Nocturnal hypoglycaemia	85.6%	77.0%	89.1%	85.9%
28.	Pharmacological induction of labour	61.7%	77.0%	63.0%	63.0%
29.	Complications of labour induction	74.7%	92.4%	76.1%	76.1%
30.	Antepartum haemorrhage (APH)	67.8%	92.3%	82.6%	72.7%
31.	Postpartum haemorrhage (PPH)	70.6%	92.4%	82.6%	74.7%
32.	Polyhydramnios	84.9%	76.9%	87.0%	84.8%
33.	Diabetic ketoacidosis (DKA)	96.6%	92.3%	93.5%	95.5%
34.	Progression of retinopathy	89.0%	84.6%	91.4%	89.2%
35.	Premature rupture of membranes (PPROM)	83.6%	84.6%	80.4%	83.0%
36.	Maternal adverse effects associated with the treatment	83.6%	92.3%	63.0%	79.5%
37.	Maternal renal failure	86.3%	92.3%	87.0%	86.8%
38.	Placental dysfunction	82.9%	84.7%	78.2%	81.9%
39.	Pre-eclampsia (PET)	95.2%	92.3%	91.2%	94.1%
40.	Haemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome	86.3%	92.3%	89.0%	87.4%
41.	Placenta praevia	65.0%	84.6%	82.6%	70.2%
42.	Placental abruption	79.5%	84.6%	84.7%	81.0%
43.	Pregnancy (gestational) induced hypertension (PIH)	91.8%	84.6%	89.2%	90.2%
44.	Worsening chronic hypertension	88.3%	92.4%	89.1%	88.8%
45.	Pulmonary oedema	72.7%	84.7%	84.8%	76.0%
46.	Excessive maternal weight gain during pregnancy	85.0%	84.6%	78.2%	83.4%
47.	Maternal death	95.2%	92.3%	80.4%	91.6%
48.	Prolonged labour	63.0%	77.0%	63.0%	63.9%
49.	Maternal infection	70.6%	77.0%	86.9%	74.7%
50.	Insulin treated in labour	76.1%	77.0%	86.9%	78.5%
51.	Maternal intensive care unit (ICU) admission	87.0%	100%	84.7%	87.3%
52.	Pulmonary embolus	72.6%	77.0%	82.6%	75.2%
Maternal life impact/ psychological					
53.	Improvement in maternal affect	50.6%	46.2%	65.2%	53.6%
54.	Improvement in fear of hypoglycaemia	56.8%	46.2%	78.3%	61.0%
55.	Diabetes distress	59.5%	46.2%	76.0%	62.4%

Chapter 4

56.	Improved self-efficacy of diabetes management	65.0%	69.3%	87.0%	70.2%
57.	Satisfaction with intervention	61.6%	61.6%	80.4%	65.8%
58.	Health related quality of life	67.1%	69.3%	78.3%	69.7%
59.	Return to normal activities	50.7%	53.9%	63.0%	53.7%
60.	Views and experiences of women	66.5%	53.9%	76.1%	67.9%
61.	Successful breastfeeding	74.0%	77.0%	58.7%	70.7%
Miscellaneous (maternal)					
62.	Trimester specific insulin dose	67.1%	69.3%	86.9%	71.7%
63.	Insulin dose at time of birth of the baby	63.1%	61.6%	86.9%	68.2%
64.	Compliance with intervention	74.7%	84.7%	84.8%	77.6%
65.	Compliance with glucose testing	76.8%	77.0%	87.0%	79.0%
66.	Number and/or duration of antepartum hospitalisation	71.9%	53.9%	67.4%	69.8%
67.	Number and/or duration of postpartum hospitalisation	60.3%	53.9%	63.0%	60.4%
68.	Onset of labour	51.3%	53.9%	63.0%	54.2%
69.	Hypoglycaemic awareness	76.7%	77.0%	91.3%	80.0%
Fetal/ infant laboratory measures					
70.	Insulin antibodies in cord blood	28.1%	38.5%	89.1%	42.5%
71.	Cord insulin like growth factor 1 (IGF-1)	31.5%	46.2%	84.7%	44.5%
72.	Cord insulin	32.9%	46.2%	80.4%	44.4%
73.	Cord C-peptide	43.8%	53.9%	84.8%	53.6%
74.	Glucose in umbilical vein	41.8%	53.9%	86.9%	52.7%
75.	Neonatal blood glucose	86.3%	84.7%	93.5%	87.8%
76.	First glucose level after birth	80.8%	84.7%	93.5%	83.9%
Fetal/ infant biometrics and anthropometrics					
77.	Birth weight	98.0%	92.3%	84.8%	96.5%
78.	Infant weight at 6 months	61.7%	69.3%	67.4%	63.4%
79.	Long bone measurements	44.6%	38.5%	78.9%	51.7%
80.	Neonatal length	66.5%	69.3%	78.3%	69.3%
81.	Abdominal circumference	71.9%	84.7%	93.5%	77.5%
82.	Infant fat mass	58.2%	46.2%	76.1%	61.5%
83.	Infant lean mass	50.7%	53.9%	71.8%	55.6%
84.	Shoulder circumference	52.1%	61.6%	69.6%	56.6%
85.	Head circumference	72.7%	77.0%	82.7%	75.0%
Fetal/ infant complications					

Chapter 4

86.	Neonatal polycythaemia	55.4%	61.6%	86.9%	62.9%
87.	Intestinal perforation	51.4%	53.9%	84.7%	59.1%
88.	Necrotising enterocolitis	55.5%	69.3%	86.9%	63.4%
89.	Intraventricular haemorrhage	57.5%	69.3%	82.6%	63.9%
90.	Periventricular leukomalacia	52.0%	69.3%	84.8%	60.4%
91.	Stillbirth	97.3%	100%	84.7%	94.6%
92.	Neonatal death	96.5%	100%	82.6%	93.6%
93.	Neonatal infection	72.5%	69.3%	91.3%	76.5%
94.	Congenital malformations	95.8%	100%	89.2%	94.6%
95.	Hypotension	48.0%	53.9%	89.1%	57.5%
96.	Hearing impairment	45.9%	61.6%	78.2%	54.2%
97.	Acute respiratory problems	79.4%	84.6%	86.9%	81.4%
98.	Apnoea	75.3%	69.3%	84.8%	77.1%
99.	Hypoxic ischaemic encephalopathy	75.4%	69.3%	86.9%	77.5%
100.	Chronic lung disease	56.8%	69.3%	84.7%	63.6%
101.	Neonatal oxygen and/or ventilatory support	74.0%	84.7%	86.9%	77.5%
102.	QTc prolongation	45.9%	69.3%	86.9%	56.6%
103.	Heart arrhythmia	50.6%	61.6%	84.7%	59.0%
104.	Shoulder dystocia	93.2%	84.6%	73.9%	88.4%
105.	Birth trauma	91.1%	84.6%	86.9%	89.8%
106.	Feeding problems	58.2%	61.6%	80.4%	63.4%
107.	Large for gestational age (LGA)	95.2%	84.6%	82.7%	91.7%
108.	Fetal macrosomia	91.1%	92.3%	89.2%	90.8%
109.	Appropriate for gestational age (AGA)	86.9%	76.9%	84.8%	85.8%
110.	Small for gestational age (SGA)	93.1%	92.2%	84.7%	91.2%
111.	Low birth weight	84.9%	92.3%	84.9%	85.4%
112.	Retinopathy of prematurity	65.1%	84.7%	89.1%	71.1%
113.	Neonatal intensive care unit (NICU) admissions	92.4%	100%	91.3%	92.7%
114.	Length of stay in neonatal intensive care unit	81.5%	92.3%	89.2%	83.8%
115.	Reduced fetal movement requiring hospitalisation	63.7%	84.7%	89.0%	70.8%
116.	Neonatal hyperbilirubinemia	71.9%	92.4%	82.6%	75.6%
117.	Seizures	72.5%	77.0%	86.9%	76.1%
118.	Neonatal hypocalcaemia	62.3%	77.0%	86.9%	68.8%
119.	Preterm birth	93.8%	100%	93.5%	94.1%

Chapter 4

120.	Neonatal hypoglycaemia	94.5%	92.3%	91.3%	93.6%
121.	Treated neonatal hypoglycaemia	89.8%	77.0%	93.5%	89.8%
Miscellaneous (Infant)					
122.	Apgar 1 min	70.5%	92.3%	86.9%	75.5%
123.	Apgar 5 min	80.8%	92.3%	89.1%	83.4%
124.	Gestational age at birth	97.2%	92.3%	89.2%	95.2%
125.	Mode of birth	93.2%	100%	78.2%	90.2%
126.	Live birth	95.2%	100%	89.1%	94.1%
127.	Infant psychomotor development	59.0%	77.0%	87.0%	66.3%
128.	Infants receiving exclusive breast milk	63.7%	77.0%	56.6%	62.9%
129.	Length and/or duration of hospitalisation	72.6%	84.7%	73.9%	73.7%
130.	Neonatal neurological optimality score	54.2%	84.7%	78.9%	61.4%
Other					
131.	Healthcare cost	61.0%	61.6%	56.5%	60.0%

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 tachypnea of the newborn, RDS-Respiratory distress syndrome, BP Blood pressure.

4.6.2 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 healthcare worker, researcher/ policymaker, and woman with PGDM/ representative respectively. Healthcare workers 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 the three rounds are shown in Table 4.2. One hundred and sixty-two (79.0%), 19 (9.3%), 10 (4.9), 6 (2.9%), 6 (2.9%) and two (1.0%) participants were from Europe, North America, Australia & New Zealand, Asia, South America and Africa respectively in round 1.

Chapter 4

Table 4.2 Country of residence and ethnicity distribution of eDelphi survey participants

	Round 1 N=205	Round 2 N=174	Round 3 N= 165
Country of Residence	n (%)	n (%)	n (%)
Argentina	5 (2.4)	4 (2.3)	3 (1.8)
Australia	7 (3.4)	7 (4.0)	6 (3.6)
Austria	4 (2.0)	4 (2.3)	4 (2.4)
Belgium	1 (0.5)	1 (0.6)	1 (0.6)
Brazil	1 (0.5)	0 (0)	0 (0)
Canada	5 (2.4)	5 (2.9)	5 (3.0)
Colombia	1 (0.5)	1 (0.6)	1 (0.6)
Croatia	1 (0.5)	1 (0.6)	1 (0.6)
Czech Republic	1 (0.5)	1 (0.6)	1 (0.6)
Denmark	6 (2.9)	6 (3.4)	6 (3.6)
Finland	2 (1.0)	2 (1.1)	2 (1.2)
France	2 (1.0)	1 (0.6)	1 (0.6)
Germany	2 (1.0)	1 (0.6)	1 (0.6)
Greece	2 (1.0)	2 (1.1)	2 (1.2)
Hungary	1 (0.5)	1 (0.6)	1 (0.6)
Ireland	113 (55.1)	100 (57.5)	95 (57.6)
Italy	9 (4.4)	6 (3.4)	5 (3.0)
Japan	2 (1.0)	2 (1.1)	2 (1.2)
The Netherlands	2 (1.0)	2 (1.1)	2 (1.2)
New Zealand	3 (1.5)	2 (1.1)	2 (1.2)
Pakistan	1 (0.5)	1 (0.6)	1 (0.6)
Poland	1 (0.5)	1 (0.6)	1 (0.6)
Saudi Arabia	3 (1.5)	1 (0.6)	1 (0.6)
Spain	1 (0.5)	1 (0.6)	1 (0.6)
South Africa	1 (0.5)	1 (0.6)	1 (0.6)
Sweden	3 (1.5)	3 (1.7)	2 (1.2)
United Kingdom	9 (4.4)	7 (4.0)	7 (4.2)
United States	15 (7.3)	9 (5.2)	9 (5.5)
Zimbabwe	1 (0.5)	1 (0.6)	1 (0.6)
Ethnicity	n (%)	n (%)	n (%)
White	162 (79.0)	141 (81.0)	131 (79.4)
Hispanic, Latino or Spanish origin	5 (2.4)	4 (2.3)	5 (3.0)
Black or African American	10 (4.9)	6 (3.5)	7 (4.2)
Asian	16 (7.8)	12 (6.9)	12 (7.3)
Middle Eastern or North African	6 (2.9)	4 (2.3)	4 (2.4)
Some other ethnicity or origin, including mixed background	13 (6.0)	17 (9.8)	18 (10.9)
Prefer not to say	3 (1.5)	0 (0)	1 (0.6)

Round 2 was completed by 174 participants, giving a retention rate of 85% from round 1. Six new outcomes were added to round 2 as they had been suggested by more than one participant in round 1, bringing the total number of outcomes for round 2 to 137. These additional outcomes were; ‘cardiovascular complications’, ‘post-partum 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 healthcare professional, researcher/ policymaker and woman with PGDM/ representative respectively.

Chapter 4

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 healthcare professionals, researchers/ policymakers and women with PGDM/ representatives respectively. Sixty-two outcomes classified as ‘consensus in’ were brought forward to the consensus meeting.

4.6.3 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; healthcare professionals (n=21), researchers/policymakers (n=3) and women with PGDM (n=2). Most of the healthcare professional also identified as researchers. Of those who identified as healthcare professionals, 11 were Endocrinologists, 6 were Obstetricians, one Midwife, one Paediatrician, one Neonatologist and one 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 three 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 discussed and addressed. A list of the final COS including 8 maternal and 11 fetal/neonatal outcomes is shown in Table 4.3. The progression of each outcome from round 2 to the end of the consensus meeting is shown in Table 4.4.

Chapter 4

Table 4.3 Final list of outcomes to be included in a COS of all future studies of treatment interventions in pregnant women with pre-gestational diabetes

Domain	Outcome
Maternal Outcomes	Trimester specific HbA1c
	Maternal weight gain during pregnancy*
	Severe hypoglycaemia
	Diabetic ketoacidosis
	Miscarriage
	Pregnancy induced hypertension
	Pre-eclampsia
Fetal/infant Outcomes	Maternal death
	Birth weight
	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'.

Chapter 4

Table 4.4 Outcomes progression from round 2 of eDelphi survey to end of consensus meeting

<i>Maternal blood/urine parameters and monitoring outcomes</i>		Round 2 Consensus →	Round 3 Consensus→	Consensus Meeting Consensus
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 hypoglycemia	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 hr urinary loss of glucose	OUT	-	-
9.	Glycaemic control	IN	IN	OUT
10.	Homeostatic model assessment- Insulin resistance (HOMA-IR)	OUT	-	-
11.	Self-measured 8-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 (TIR)	IN	IN	OUT
20.	Glycaemic variability	IN	OUT	-
21.	Proteinuria	IN	IN	OUT
<i>Maternal Complications Outcomes</i>		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
22.	Ectopic pregnancy	OUT	-	
23.	Miscarriage	IN	IN	IN
24.	Pregnancy termination	OUT	-	-
25.	Maternal hypoglycaemia	IN	IN	OUT

Chapter 4

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 (APH)	IN	OUT	-
31.	Postpartum haemorrhage (PPH)	IN	OUT	-
32.	Polyhydramnios	IN	IN	OUT
33.	Diabetic ketoacidosis (DKA)	IN	IN	IN
34.	Progression of retinopathy	IN	IN	OUT
35.	Premature rupture of membranes (PPROM)	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 (PET)	IN	IN	IN
40.	Haemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome	IN	IN	OUT
41.	Placenta praevia	OUT	-	-
42.	Placental abruption	IN	IN	OUT
43.	Pregnancy (gestational) induced hypertension (PIH)	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	-	-
50.	Maternal infection	IN	OUT	-
51.	Insulin treated in labour	IN	OUT	-
52.	Maternal intensive care unit (ICU) admission	IN	IN	OUT
53.	Pulmonary embolus	IN	OUT	-
Maternal Life Impact/ Psychological Outcomes		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
54.	Improvement in maternal affect	OUT	-	-
55.	Post-partum depression*	OUT	-	-
56.	Improvement in fear of hypoglycaemia	OUT	-	-
57.	Diabetes distress	OUT	-	-
58.	Diabetes burnout*	OUT	-	-

Chapter 4

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 Maternal Outcomes		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
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
Fetal/ Infant Laboratory Measures Outcomes		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
74.	Insulin antibodies in cord blood	OUT	-	-
75.	Cord insulin like growth factor 1 (IGF-1)	OUT	-	-
76.	Cord insulin	OUT	-	-
77.	Cord C-peptide	OUT	-	-
78.	Glucose in umbilical vein	OUT	-	-
79.	Neonatal blood glucose	IN	IN	OUT
80.	First glucose level after birth	IN	IN	OUT
Fetal/ Infant Biometrics and Anthropometrics Outcomes		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
81.	Birth weight	IN	IN	IN
82.	Infant weight at 6 months	OUT	-	-
83.	Long bone measurements	OUT	-	-
84.	Neonatal length	OUT	-	-
85.	Abdominal circumference	IN	IN	OUT
86.	Infant fat mass	OUT	-	-
87.	Infant lean mass	OUT	-	-

Chapter 4

88.	Shoulder circumference	OUT	-	
89.	Head circumference	IN	IN	
<i>Fetal/ Infant Complications Outcomes</i>		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
90.	Neonatal polycythaemia	OUT	-	-
91.	Intestinal perforation	OUT	-	-
92.	Necrotising enterocolitis	OUT	-	-
93.	Intraventricular haemorrhage	IN	OUT	-
94.	Periventricular leukomalacia	OUT	-	-
95.	Reduced fetal movement requiring hospitalisation	IN	OUT	-
96.	Stillbirth	IN	IN	IN
97.	Neonatal death	IN	IN	IN
98.	Neonatal infection	IN	IN	OUT
99.	Congenital malformations	IN	IN	IN
100.	Hypotension	OUT	-	-
101.	Hearing impairment	OUT	-	-
102.	Acute respiratory problems	IN	IN	OUT
103.	Apnoea	IN	IN	OUT
104.	Hypoxic ischaemic encephalopathy	IN	IN	OUT
105.	Chronic lung disease	OUT	-	-
106.	Neonatal oxygen and/or ventilatory support	IN	IN	OUT
107.	QTc prolongation	OUT	-	-
108.	Heart arrhythmia	OUT	-	-
109.	Shoulder dystocia	IN	IN	IN
110.	Birth trauma	IN	IN	OUT
111.	Feeding problems	OUT	-	-
112.	Large for gestational age (LGA)	IN	IN	IN
113.	Fetal macrosomia	IN	IN	OUT
114.	Appropriate for gestational age (AGA)	IN	IN	OUT
115.	Small for gestational age (SGA)	IN	IN	IN
116.	Low birth weight	IN	IN	OUT
117.	Retinopathy of prematurity	IN	OUT	-
118.	Neonatal intensive care unit (NICU) admissions	IN	IN	OUT
119.	Length of stay in neonatal intensive care unit	IN	IN	OUT
120.	Neonatal hyperbilirubinemia	IN	IN	OUT

Chapter 4

121.	Seizures	IN	IN	OUT
122.	Neonatal hypocalcaemia	IN	OUT	-
123.	Preterm birth	IN	IN	IN
124.	Neonatal hypoglycaemia	IN	IN	IN
125.	Treated neonatal hypoglycaemia	IN	IN	OUT
126.	Offspring incidence of diabetes*	IN	OUT	-
<i>Infant Miscellaneous Outcomes</i>		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
127.	Apgar 1 min	IN	OUT	-
128.	Apgar 5 min	IN	IN	OUT
129.	Gestational age at birth	IN	IN	IN
130.	Mode of birth	IN	IN	IN
131.	Live birth	IN	IN	OUT
132.	Infant psychomotor development	OUT	-	-
133.	Infants receiving exclusive breast milk	OUT	-	-
134.	Length and/or duration of hospitalisation	IN	OUT	-
135.	Neonatal neurological optimality score	OUT	-	-
<i>Other</i>		Round 2 Consensus	Round 3 Consensus	Consensus Meeting Consensus
136.	Healthcare cost	OUT	-	-
137.	Out of pocket cost of treatment*	IN	OUT	-

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

Outcome rephrased to ‘maternal weight gain during pregnancy’ at the consensus meeting

Three outcomes (‘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 (CGM) data were available. It was recommended that these outcomes can be reported in CGM studies in addition to this COS.

Some outcomes although deemed important were excluded from the COS after discussion. For example, ‘Polyhydramnios’ was excluded because it is typically considered a surrogate marker for adverse pregnancy outcomes, rather than an endpoint in itself. ‘Progression of retinopathy’ was excluded because not all studies (especially those based in emerging economies) can measure this outcome and thus would limit acceptability. ‘Neonatal intensive care unit (NICU)

Chapter 4

admissions' was excluded because of differences in criteria for admission of infants to NICU. Outcomes excluded because of lack of universally agreed definitions include: '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 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.

4.7 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 reduce outcome reporting heterogeneity and bias. This will help 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 as the aim of the 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 as prior COS studies by our group in the area of maternal diabetes from these databases yielded comprehensive results^{86, 166}. We limited our search to the English language which may have introduced selection bias. However, in round one of the eDelphi survey, we gave participants the opportunity to add additional 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

Chapter 4

literature in how to define, extract, group, and count trial outcomes¹⁵⁵. 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 (PPI)¹⁶⁷. Therefore, women with a history of PGDM 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 healthcare professionals/researchers in both the eDelphi process and the consensus meeting. In this study, the consensus meeting was represented mainly by healthcare professionals/researchers but also included two women. This has the potential to introduce bias. However, during the consensus meeting, women shared experiences of outcomes that were important to them. In doing so, the group took on board patients' unique point of view prior to 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 patients¹⁶⁸. The COMET People and Patient Participation, Involvement and Engagement (PoPPIE) working group has been established within the initiative 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 COSs¹⁶⁹. 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 (LMIC) participants¹⁷⁰. However, the outcomes listed in the final COS (table 4.4) are for the most part easily measured and recorded globally. This will make the COS globally applicable where studies performed in LMIC can adapt the COS in addition to their specific outcomes of interest.

Chapter 4

There is no consensus regarding study sample size appropriate for COS development. Prior COS work by our group involved 173 and 288 participants respectively after round one ^{86, 166}. In this study, we had 205 participants after round one. There were low attrition rates between rounds of the eDelphi survey (15% round one to two and 5% round two to three).

All outcomes satisfying the inclusion criteria from round three were brought forward to a consensus meeting where an international audience with expertise in maternal diabetes participated in decision making for the final COS. Adapting to the current social distancing measures in the setting of a COVID-19 pandemic, we conducted a successful online global 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 RCTs assessing treatment interventions in pregnant women with PGDM is heterogenous 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 ‘how it should be measured’. A general plain English definition of each outcome was provided during both the eDelphi survey stage and consensus meeting in order to assist those unfamiliar with medical terms to make informed decisions. This COS highlights the importance of a common language and is complementary to prior work by Feig et al which provides a repository of a set of definitions for clinical outcomes in diabetes in pregnancy ⁶⁵.

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 ⁶⁶. 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 HbA1c measurement, all of the outcomes listed in the COS are primarily observational and thus would not require additional resources.

Chapter 4

The James Lind Alliance (JLA) through the Diabetes and Pregnancy Priority Setting Partnership (PSP) 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 impact¹⁵⁶. For diabetes in pregnancy, a significant number of these research questions will assess interventions to improve outcomes for both mother and baby. Thus, it is now timely to entrench this COS in the research in order to make meaningful comparisons between interventions in the future.

4.8 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 improve trial reporting and minimise research waste by prioritising the collection and reporting of outcomes that matter to all relevant stakeholder group. 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 babies. 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 in the future and has the ability for increased participation from low- and middle-income countries.

Chapter 5

Chapter 5: Other Contributions

5.1 Chapter Introduction

This chapter discusses two pieces of work I also contributed to and which are now published. Paper 4 presents a Core Outcome Set (COS) for studies of Gestational Diabetes Mellitus (GDM) prevention and treatment. Paper 5 presents a review of COSs for studies of diabetes in pregnancy.

5.2 Paper 4: A Core Outcome Set for Studies of Gestational Diabetes Mellitus Prevention and Treatment

Egan, A.M., Bogdanet, D., Griffin, T.P., Kgosidialwa O. et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. Diabetologia 63, 1120–1127 (2020). <https://doi.org/10.1007/s00125-020-05123-6>.

Chapter 5

5.2.1 Abstract

Aims/Hypothesis The aim of this systematic review was to develop core outcome sets (COSs) for trials evaluating interventions for the prevention or treatment of gestational diabetes mellitus (GDM).

Methods We identified previously reported outcomes through a systematic review of the literature. These outcomes were presented to key stakeholders (including patient representatives, researchers and clinicians) for prioritisation using a three-round, e-Delphi study. A priori consensus criteria informed which outcomes were brought forward for discussion at a face-to-face consensus meeting where the COS was finalised.

Results Our review identified 74 GDM prevention and 116 GDM treatment outcomes, which were presented to stakeholders in round 1 of the e-Delphi study. Round 1 was completed by 173 stakeholders, 70% (121/173) of whom went on to complete round 2; 84% (102/121) of round 2 responders completed round 3. Twenty-two GDM prevention outcomes and 30 GDM treatment outcomes were discussed at the consensus meeting. Owing to significant overlap between included prevention and treatment outcomes, consensus meeting stakeholders agreed to develop a single prevention/treatment COS. Fourteen outcomes were included in the final COS. These consisted of six maternal outcomes (GDM diagnosis, adherence to the intervention, hypertensive disorders of pregnancy, requirement and type of pharmacological therapy for hyperglycaemia, gestational weight gain and mode of birth) and eight neonatal outcomes (birthweight, large for gestational age, small for gestational age, gestational age at birth, preterm birth, neonatal hypoglycaemia, neonatal death and stillbirth).

Conclusions/interpretation This COS will enable future GDM prevention and treatment trials to measure similar outcomes that matter to stakeholders and facilitate comparison and combination of these studies.

Trial registration This study was registered prospectively with the Core Outcome Measures in Effectiveness Trials (COMET) database.

Chapter 5

5.2.2 Introduction

Gestational diabetes mellitus (GDM) is diabetes with onset or first recognition during pregnancy that was clearly not overt diabetes prior to gestation¹⁷¹. It affects 18.4 million pregnancies worldwide annually¹⁷². GDM is associated with an increased risk of adverse pregnancy outcomes including pre-eclampsia and Caesarean delivery for the mother and neonatal hypoglycaemia, large for gestational age and birth trauma for the infant¹⁷³⁻¹⁷⁷. These offspring are at increased risk of diabetes and obesity^{178, 179} during childhood and adulthood and the mothers have a significantly elevated risk of type 2 diabetes^{180, 181}.

Over the past two decades, the burden of GDM has driven an increase in randomised trials of interventions for the prevention and treatment of GDM^{182, 183}. However, heterogeneity in outcomes reported in these trials makes combining and comparing results difficult¹⁸⁴. As a result, evidence synthesis and meta-analyses become less efficient and the reliability of evidence to guide healthcare decisions is limited¹⁸⁵. One approach to address this lack of uniformity is to develop a core outcome set (COS) or an agreed set of outcomes⁸⁵. A COS represents a minimum set of outcomes that are expected to be measured and reported in all trials in specific areas of healthcare; however, researchers may report additional outcomes at their discretion. Typically, COSs are also suitable for use in relevant clinical audits and observational studies¹⁸⁶. The Core Outcome Measures in Effectiveness Trials (COMET) initiative brings together current thinking and provides methodological guidance on this subject^{186, 187}. In the field of women's health, over 50 journals endorse the Core Outcomes in Women's Health (CROWN) initiative, which promotes COS development and effective dissemination of related manuscripts¹⁸⁷.

The aim of this study was to develop COSs for studies evaluating the effectiveness of interventions for the prevention or treatment of GDM.

5.2.3 Methods

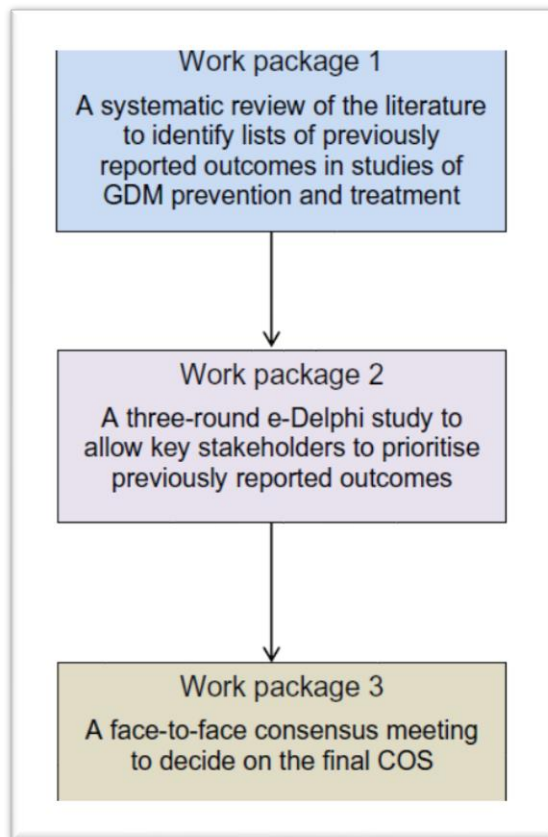
This study was registered prospectively with the COMET database (<http://www.comet-initiative.org/studies/details/686/>) and a detailed protocol is published⁸⁹. The study design was guided by the COMET initiative and COSSTAD recommendations^{186, 188}. Ethical approval for the study was obtained from the Galway University Hospitals ethics committee.

The study was conducted within three work packages (Fig.1): (1) a systematic review of the literature to identify previously reported outcomes; (2) a three-round, web-based, e-Delphi

Chapter 5

survey with key stakeholders to prioritise outcomes; and (3) a consensus meeting to finalise the COS.

Figure 5.1 Summary of the study work packages



Two separate procedures were originally planned and conducted: one for GDM prevention and one for GDM treatment. However, the results from these separate consensus procedures were very similar and stakeholders at the consensus meeting decided to produce a single COS for all studies of GDM prevention or treatment.

Systematic review

The search strategy is outlined in the study protocol. In brief, the following databases were searched for relevant studies: MEDLINE; Embase; Web of Science; Cochrane Library; and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We included randomised trials and systematic reviews of randomised trials (with and without meta-analyses) comparing the effectiveness of pharmacological and non-pharmacological interventional strategies for both prevention and treatment of GDM. Given the large number of previously published studies, a pragmatic approach was taken and the systematic review was performed

Chapter 5

in stages until outcome saturation was reached. In this regard, the initial search included time limits of publication between January 2015 and February 2019. Two reviewers (AME and DB) assessed the titles and abstracts of identified studies independently. Full texts of studies meeting the inclusion criteria (or where this was uncertain) were retrieved and consensus was reached on inclusion status. Studies were divided into those for prevention and those for treatment of GDM. Outcomes were extracted and grouped under three major domains following review by the study advisory group (see study protocol)⁸⁶: maternal outcomes; neonatal outcomes; and other outcomes.

e-Delphi Study

We conducted a three-round, e-Delphi study using SurveyMethods software (www.surveymethods.com, accessed 16 April 2019). Participants were recruited from the following groups: (1) women representatives (pregnant women at risk of GDM, with GDM or women with a history of GDM); (2) healthcare professionals (professionals who care for women with GDM); and researchers (researchers and policy makers with an active interest in GDM). We sent an e-mail explaining the study and inviting participation through an electronic link to the list managers of the following organisations: International Association of the Diabetes and Pregnancy Study Groups (IADPSG); Diabetes Ireland (DI); Irish Endocrine Society (IES); ADA; EASD; the Irish Midwifery e-Group; and the Diabetic Pregnancy Study Group (DPSG) of the EASD. We also circulated information about the study on social media and to women with diabetes attending antenatal clinics at University Hospital Galway, Galway, Ireland. Potential participants were invited to forward the invitation to others whom they regarded as having the required expertise. An e-mail reminder was sent to anyone who did not respond after 10 days and again after 14 days.

The round 1 survey included a further explanation of the study with a consent process and followed with a short questionnaire that requested participant demographic data including the stakeholder group that best represented their profile. It also presented the outcomes identified in the review and participants were asked to rate each outcome for GDM prevention and treatment separately on a nine-point Likert scale with higher values representing increased importance for inclusion in the COS. There was an 'unable to score' option that could be selected for each outcome. All outcomes were accompanied by a plain English explanation. Participants were invited to submit up to two additional outcomes for GDM prevention and

Chapter 5

two additional outcomes for GDM treatment that they considered important or relevant for inclusion in the COS¹⁸⁹. The results from round 1 were summarised using descriptive statistics and all outcomes were carried forward to round 2 including additional outcomes that were suggested by more than one participant. Participants who completed round 1 were invited to participate in round 2. In this second round, participants were provided with their scores from round 1 and with the distribution of scores for each outcome per stakeholder group. They were asked to re-score the outcomes after considering the information provided from round 1. Outcomes were classified as ‘consensus in’ ($\geq 70\%$ participants giving scores of 7–9 and $< 15\%$ scoring 1–3), ‘consensus out’ ($\leq 50\%$ participants scoring 7–9 in each stakeholder group) or ‘no consensus’ (anything else). All outcomes scored as ‘consensus in’ were carried forward to round 3. All participants who completed rounds 1 and 2 were invited to participate in round 3. Again, participants were provided with their scores from round 2 and the distribution of scores per stakeholder group. Participants were asked to re-score the outcomes.

Consensus meeting

A face-to-face consensus meeting took place on 5 September 2019 in Graz, Austria. The aim was to agree on the final outcomes to be included in the COS. The meeting was moderated by an experienced chairperson (DD) who did not vote at the meeting. Outcomes classified as ‘consensus in’ or ‘no consensus’ in the e-Delphi round 3 were presented at the meeting along with the responses per stakeholder group. An open discussion took place on each outcome. There was opportunity to combine or modify individual outcomes and participants were encouraged to consider whether each outcome was applicable to GDM treatment or GDM prevention or both. Participants were then asked to vote on each outcome as ‘yes’ or ‘no’ for inclusion in the COS. Participants used Poll Everywhere (www.pollerywhere.com, accessed 16 October 2019) to vote anonymously. An outcome was included in the final COS when $\geq 70\%$ participants voted ‘yes’.

5.2.4 Results

Systematic Review

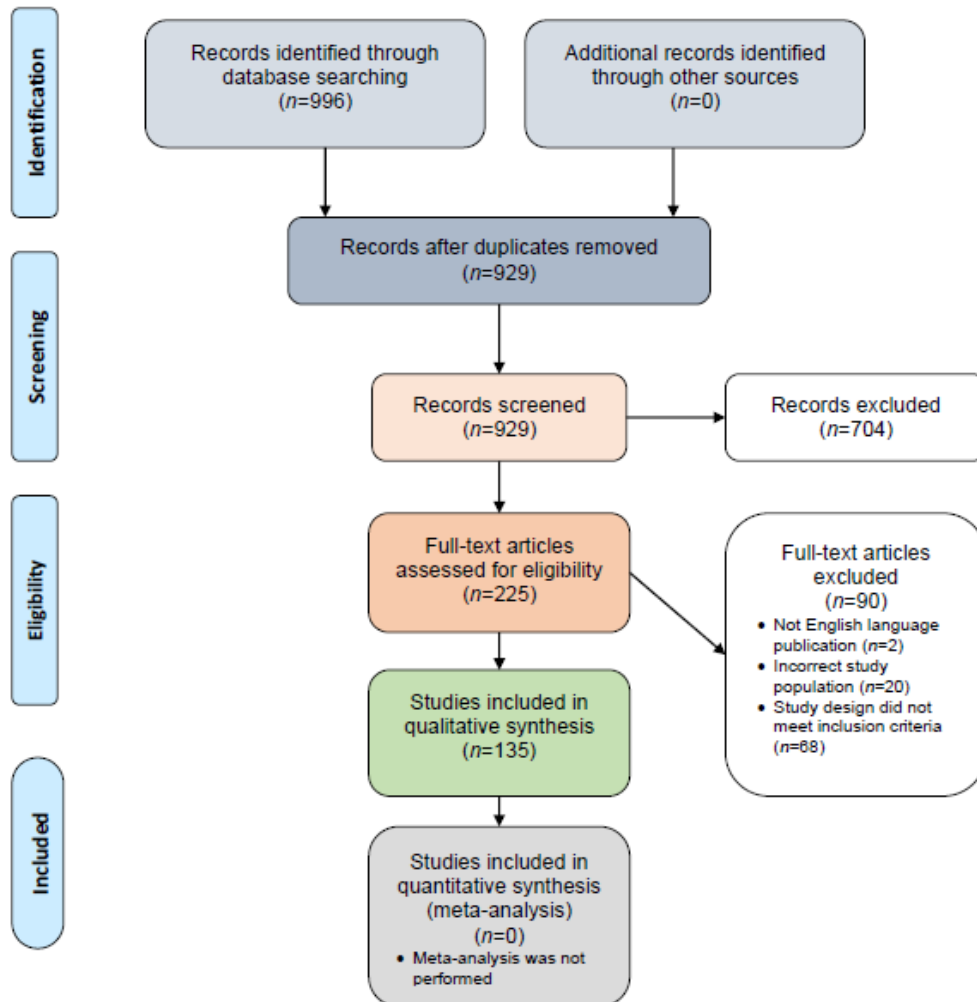
Figure 5.2 shows the PRISMA flow diagram which illustrates the flow of information through the different phases of the systematic review. A total of 929 potentially relevant studies were retrieved. Following review of the title and abstract, 225 full text papers were retrieved and assessed. Ninety papers were excluded following assessment and 135 papers were included in

Chapter 5

the review. Of the 135 papers identified, 45 related to GDM prevention and 90 related to GDM treatment (Figure 5.3). Appendix 2 lists all included studies. Outcomes from 2017– 2019 studies were indexed initially followed by outcomes from 2016 and 2015. During extraction of 2015 outcomes, saturation was reached, with no new additional outcomes identified during this time period. Extracted outcomes were reviewed by the study advisory group to ensure removal of duplicate outcomes, combine similar outcomes and clarify outcome terminology. Following this, 74 GDM prevention outcomes and 116 GDM treatment outcomes were listed for inclusion in round 1 of the e-Delphi Study (Table 5.1).

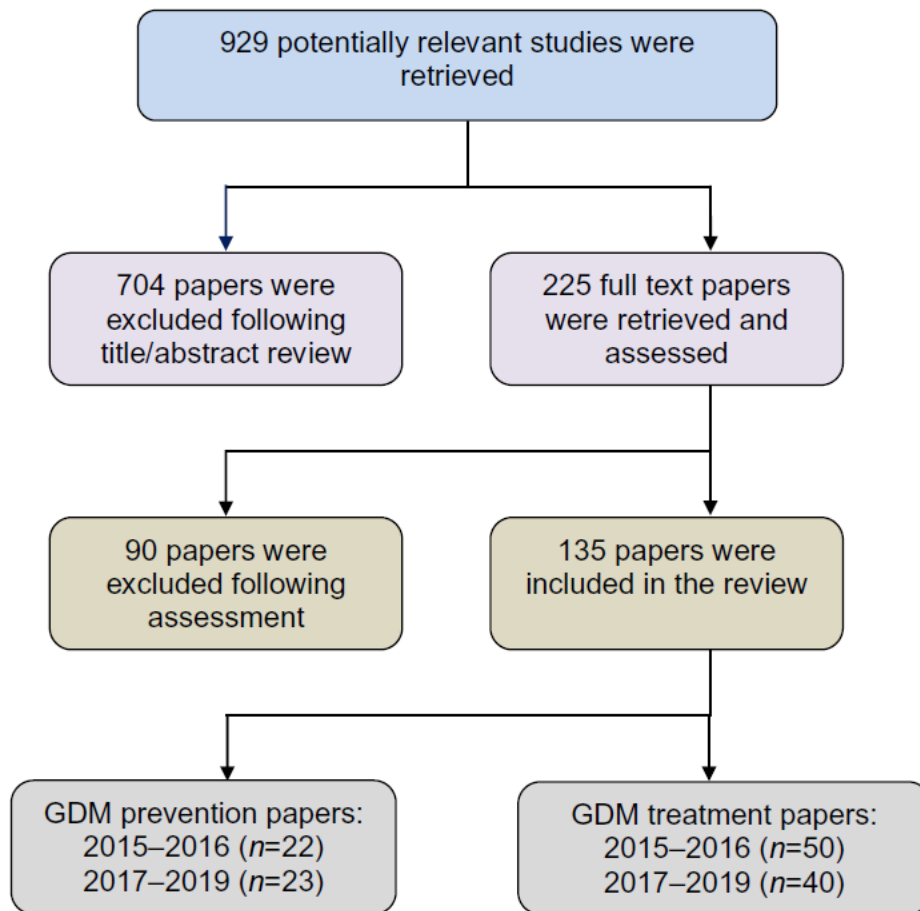
Chapter 5

Figure 5.2 PRISMA flow diagram of the systematic review



Chapter 5

Figure 5.3 Selection of studies for systematic review



Chapter 5

Table 5.1 Outcomes included in e-Delphi round 1 and number and percentage of respondents giving each outcome a “high” score of 7-9

Prevention Outcome	Group 1: Patient Representatives		Group 2: Health Care Professionals		Group 3: Researchers	
	n= 23	%	n = 116	%	n= 34	%
1. Maternal Outcomes						
GDM Diagnosis	21	91%	108	93%	32	94%
Gestational Weight Gain	17	74%	93	80%	26	76%
Increase in BMI during pregnancy	13	57%	72	62%	21	62%
Body Composition	12	52%	41	35%	14	41%
Skin Fold thickness	9	39%	30	26%	12	35%
Waist Circumference	12	52%	44	38%	15	44%
Postpartum weight retention	14	61%	79	68%	26	76%
Requirement for insulin therapy	20	87%	105	91%	32	94%
Blood pressure	17	74%	88	76%	28	82%
Hypertensive disorders of pregnancy	20	87%	90	78%	30	88%
Maternal hospitalisation	12	52%	71	61%	24	71%
Placental abruption	17	74%	59	51%	23	68%
Dietary intake	18	78%	91	78%	24	71%
Physical activity	16	70%	90	78%	24	71%
Self-rated health	13	57%	63	54%	21	62%
Quality of life	16	70%	74	64%	23	68%
Self-rated diet	12	52%	54	47%	15	44%
Induction of labour	11	48%	63	54%	20	59%
Mode of birth	15	65%	81	70%	28	82%
Termination of pregnancy	7	30%	56	48%	16	47%
Miscarriage	14	61%	66	57%	18	53%
Maternal accident	12	52%	31	27%	10	29%
Maternal sepsis	14	61%	57	49%	19	56%
Hospitalisation during the pregnancy	13	57%	62	53%	21	62%
Admission to the HDU	14	61%	67	58%	23	68%
Intrapartum haemorrhage	15	65%	52	45%	19	56%
Postpartum haemorrhage	15	65%	54	47%	23	68%
Perineal trauma	10	43%	59	51%	23	68%
Fasting blood glucose	18	78%	103	89%	30	88%
Postprandial glucose	18	78%	97	84%	27	79%
Insulin	17	74%	58	50%	22	65%
Hba1c	18	78%	91	78%	28	82%
C peptide	14	61%	57	49%	15	44%
Ferritin	12	52%	33	28%	14	41%
Maternal lipid profile	12	52%	59	51%	14	41%
Haemoglobin	12	52%	43	37%	11	32%
High sensitivity CRP	13	57%	30	26%	9	26%
HOMA-IR	15	65%	59	51%	20	59%
IL-6	11	48%	24	21%	6	18%
Leptin	11	48%	27	23%	4	12%
Cortisol	11	48%	30	26%	5	15%
Non-esterified fatty acids	9	39%	27	23%	9	26%
Ratio of plasminogen activator inhibitor 1 to 2	9	39%	23	20%	13	38%
Vitamin D level	13	57%	45	39%	6	18%
2. Neonatal Outcomes						
Preterm birth	17	74%	83	72%	31	91%
Gestational week at birth	17	74%	95	82%	32	94%
Neonatal death	18	78%	91	78%	31	91%
Stillbirth	18	78%	90	78%	31	91%
Small for gestational age	16	70%	87	75%	30	88%
Large for gestational age	18	78%	101	87%	33	97%

Chapter 5

Macrosomia	16	70%	94	81%	29	85%
Birthweight	19	83%	99	85%	32	94%
Skinfold thickness	14	61%	44	38%	17	50%
Baby anthropometry	17	74%	74	64%	25	74%
% body fat neonate	13	57%	50	43%	19	56%
APGAR	15	65%	77	66%	27	79%
Ponderal index	10	43%	55	47%	20	59%
Respiratory distress	16	70%	75	65%	26	76%
Hyperbilirubinemia	13	57%	73	63%	25	74%
Congenital malformation	14	61%	82	71%	26	76%
Brachial plexus injury	12	52%	89	77%	29	85%
Bone fracture	13	57%	76	66%	27	79%
Shoulder dystocia	11	48%	94	81%	28	82%
Neonatal sepsis	15	65%	67	58%	21	62%
Retinopathy of prematurity	14	61%	54	47%	18	53%
Neonatal hypoglycaemia	18	78%	99	85%	29	85%
Neonatal internal haemorrhage	16	70%	60	52%	18	53%
Need for mechanical ventilation	16	70%	71	61%	20	59%
Necrotising enterocolitis	15	65%	54	47%	19	56%
Admission to neonatal ICU	16	70%	91	78%	27	79%
Number of days in special baby care unit	13	57%	83	72%	27	79%
Number of days in hospital	13	57%	79	68%	25	74%
Discharge home on oxygen	13	57%	52	45%	16	47%
3. Other Outcomes						
Health cost analysis	14	61%	71	61%	23	68%

Treatment Outcome	n = 23	%	n = 116	%	n = 34	%
1. Maternal Outcomes						
Quality of life score	15	65%	68	59%	24	71%
Self-care behaviour	17	74%	67	58%	19	56%
Satisfaction with treatment	15	65%	71	61%	22	65%
Empowerment	16	70%	63	54%	16	47%
Self-efficacy	14	61%	60	52%	18	53%
Health related quality of life	14	61%	62	53%	22	65%
Compliance with self-monitoring	16	70%	85	73%	23	68%
Depression	16	70%	68	59%	28	82%
Stress	18	78%	66	57%	21	62%
Post-natal depression	15	65%	69	59%	26	76%
Adherence to the intervention	15	65%	85	73%	28	82%
Behaviour change associated with the intervention	16	70%	77	66%	23	68%
Anxiety	16	70%	59	51%	21	62%
Cost of treatment	13	57%	75	65%	25	74%
Acceptability of treatment	14	61%	81	70%	29	85%
Vitamin D level	12	52%	53	46%	13	38%
Glucose fasting	18	78%	90	78%	28	82%
1 hour glucose tolerance test result	19	83%	80	69%	24	71%
2 hour glucose tolerance test result	19	83%	91	78%	28	82%
Post-prandial glucose level	18	78%	83	72%	22	65%
Average glucose level	17	74%	63	54%	20	59%
% glucose measurements out of range	17	74%	75	65%	17	50%
Time to control of glucose level	17	74%	71	61%	17	50%
Insulin level	17	74%	41	35%	16	47%
HbA1c	18	78%	82	71%	23	68%
HOMA-IR	15	65%	49	42%	15	44%
Very low density lipoprotein cholesterol	11	48%	44	38%	14	41%

Chapter 5

Free fatty acids	12	52%	39	34%	14	41%
Lipid profile	12	52%	54	47%	17	50%
High sensitivity CRP	13	57%	34	29%	14	41%
QUICKI	14	61%	35	30%	12	35%
C peptide	13	57%	36	31%	10	29%
Carbohydrate intake per day	17	74%	72	62%	22	65%
Protein intake per day	16	70%	64	55%	19	56%
Fat intake per day	13	57%	62	53%	21	62%
Blood pressure	19	83%	83	72%	26	76%
HELLP Syndrome	14	61%	70	60%	24	71%
Hypertensive disorders of pregnancy	16	70%	78	67%	29	85%
Number of hospitalisations	12	52%	75	65%	25	74%
Polyhydramnios	16	70%	82	71%	22	65%
Placental abruption	16	70%	68	59%	23	68%
Requirement for insulin	18	78%	92	79%	29	85%
Gestational age at insulin therapy	15	65%	89	77%	26	76%
Total daily insulin dose	19	83%	81	70%	25	74%
Requirement for metformin	17	74%	81	70%	21	62%
Requirement for pharmacological therapy for hyperglycaemia	18	78%	89	77%	29	85%
Hypoglycaemia	15	65%	78	67%	27	79%
Treatment failure	16	70%	80	69%	28	82%
Gestational weight gain	17	74%	89	77%	30	88%
Change in BMI	19	83%	70	60%	21	62%
Maternal weight at time of birth	16	70%	76	66%	22	65%
Return to prepregnancy weight	17	74%	76	66%	24	71%
Induction of labour	14	61%	70	60%	21	62%
Prolonged labour	12	52%	52	45%	19	56%
Duration of labour	12	52%	54	47%	15	44%
Premature rupture of membranes	12	52%	54	47%	17	50%
Birth complication	17	74%	79	68%	28	82%
Mode of birth	15	65%	81	70%	29	85%
Reason for caesarean birth	15	65%	82	71%	27	79%
Perineal trauma	12	52%	71	61%	22	65%
Blood loss during birth	14	61%	48	41%	19	56%
Post-partum haemorrhage	15	65%	59	51%	21	62%
Chorioamnionitis	13	57%	55	47%	17	50%
Maternal ICU admission	14	61%	74	64%	26	76%
Postpartum infection	13	57%	59	51%	22	65%
Breast feeding	14	61%	78	67%	29	85%
Maternal mortality	16	70%	82	71%	31	91%
Maternal serious morbidity	16	70%	83	72%	29	85%
Development of type 2 diabetes	19	83%	94	81%	32	94%
Post pregnancy weight	17	74%	83	72%	26	76%
2. Neonatal Outcomes						
Fetal growth restriction	14	61%	82	71%	25	74%
Macrosomia	16	70%	87	75%	26	76%
Birthweight	16	70%	91	78%	31	91%
Large for gestational age	15	65%	90	78%	31	91%
Small for gestational age	13	57%	84	72%	30	88%
Gestational age at birth	17	74%	92	79%	29	85%
Preterm birth	16	70%	83	72%	22	65%
Neonatal arm circumference	11	48%	48	41%	14	41%
Birth length	12	52%	57	49%	21	62%
Neonatal chest circumference	11	48%	40	34%	17	50%
Neonatal head circumference	12	52%	52	45%	20	59%
APGAR	15	65%	72	62%	28	82%
Congenital malformation	15	65%	76	66%	25	74%

Chapter 5

Pondoral index	14	61%	54	47%	21	62%
Shoulder dystocia	13	57%	86	74%	26	76%
Bone fracture	13	57%	70	60%	25	74%
Brachial plexus injury	13	57%	75	65%	27	79%
Neonatal mortality	15	65%	86	74%	28	82%
Birth trauma	15	65%	82	71%	27	79%
Neonatal hypoglycaemia	16	70%	93	80%	28	82%
Need for IV glucose	18	78%	83	72%	25	74%
Neonatal glucose level	18	78%	76	66%	24	71%
Neonatal sepsis	14	61%	63	54%	23	68%
Neonatal respiratory distress syndrome	14	61%	74	64%	24	71%
Transient tachypnoea of the newborn	13	57%	65	56%	21	62%
Bronchopulmonary dysplasia	13	57%	51	44%	17	50%
Neonatal internal haemorrhage	13	57%	53	46%	17	50%
Necrotising enterocolitis	12	52%	48	41%	15	44%
Hyperbilirubinemia	11	48%	66	57%	23	68%
Need for phototherapy	11	48%	60	52%	20	59%
Neonatal intensive care unit admission	15	65%	80	69%	25	74%
Infant sex	9	39%	50	43%	21	62%
Neonatal hypocalcaemia	13	57%	45	39%	14	41%
Umbilical cord PH	11	48%	56	48%	14	41%
Miscarriage	14	61%	69	59%	23	68%
Neonatal mortality	15	65%	85	73%	29	85%
Neonatal hospitalisation	14	61%	78	67%	27	79%
Livebirth	16	70%	81	70%	28	82%
Stillbirth	16	70%	82	71%	29	85%
Perinatal death	16	70%	85	73%	29	85%
Diabetes in adulthood	17	74%	81	70%	26	76%
Adiposity in adulthood	16	70%	74	64%	22	65%
Neurosensory disability in later childhood	14	61%	55	47%	18	53%
Childhood adiposity	14	61%	74	64%	23	68%
Neonatal adiposity	14	61%	70	60%	23	68%
Childhood BMI	14	61%	71	61%	21	62%

e-Delphi Study

Round one was completed by 173 stakeholders (n = 132, 76% female sex; n = 39, 23% male sex; n = 2, 1.0% did not disclose sex). All participants gave informed consent prior to participating. There was international distribution of participants with 27 countries and six continents represented (Table 5.2). A total of 69 (40%) respondents were from Ireland, 20 (12%) were from Canada and 16 (9%) from the USA. Stakeholders represented three broad categories: patient representatives (n = 23, 13%); healthcare professionals (n = 116, 67%); and researchers (n = 34, 19%). Within the group who self-identified as ‘healthcare professionals’, there was representation from the following disciplines: anaesthesiology; midwifery; specialist midwifery; dietetics; endocrinology; general practice; neonatology; specialist nursing; obstetric medicine; obstetrics; paediatrics; pharmacy; and physiotherapy.

Chapter 5

The round 2 survey again presented the lists of GDM prevention outcomes and GDM treatment outcomes. One additional outcome (breastfeeding) was included in the list of GDM prevention outcomes as it was suggested by more than one participant in round 1. Round 2 was completed by 70% (121/173) of those who had completed the first survey as follows: patient representatives, n = 19 (16%); healthcare professionals, n = 70 (58%); and researchers, n = 32 (26%). A total of 22 GDM prevention outcomes and 30 GDM treatment outcomes were classified as ‘consensus in’ and were carried forward to round 3 (Table 5.3). Round 3 was completed by 84% (102/121) of those who had completed round 2 as follows: patient representatives, n = 16 (16%); healthcare professionals, n = 56 (55%); and researchers, n = 30 (29%). Following analysis of round 3, all outcomes were classified as ‘consensus in’ or ‘no consensus’ and therefore all 22 GDM prevention and 30 GDM treatment outcomes were carried forward to the face-to-face consensus meeting.

Consensus Meeting

The panel consisted of 23 participants, representing a variety of countries, who had volunteered to take part in the e-Delphi study or who had been sampled purposefully by the study advisory group. The participants included representatives from each of the three stakeholder groups: patient representatives (n = 6); healthcare professionals (n = 10); and researchers (n = 7). In addition to the non-voting chairperson, there were two administrators responsible for recording the discussion and poll results. Table 5.3 outlines the results of the voting at the consensus meeting for each outcome. Based on the views of the group, the treatment outcome listed as ‘requirement for pharmacological therapy for hyperglycaemia’ was rephrased to ‘requirement and type of pharmacological therapy for hyperglycaemia’ and the treatment outcome listed as ‘perinatal mortality’ was changed to ‘neonatal death’. Following the voting process, 11 outcomes were included in the GDM prevention COS and 13 were included in the GDM treatment COS (Table 5.3). All eight chosen outcomes from the neonatal domain were identical between the prevention and treatment COSs. The GDM treatment COS contained two additional outcomes that were not included in the GDM prevention COS. These were ‘adherence to the intervention’ and ‘mode of birth’. Following a further discussion and vote, these outcomes were included in the GDM prevention COS. Finally, the prevention outcome ‘GDM diagnosis’ was (appropriately) not included in the GDM treatment COS.

Chapter 5

Given the fact that there was agreement on all other outcomes between the two COSs, it was decided that a single COS for the prevention and/or treatment of GDM would be ideal and would likely increase uptake of the COS. Table 5.4 outlines the final COS, which includes six maternal and eight neonatal outcomes. The outcome ‘GDM prevention’ is highlighted as relevant to GDM prevention studies only.

Table 5.2 e-Delphi round 1 participants

Country of Residence	Number of participants	% Participants
Argentina	9	5.2%
Australia	3	1.7%
Austria	6	3.5%
Canada	20	11.6%
China	1	0.6%
Colombia	1	0.6%
Denmark	6	3.5%
UK	8	4.6%
France	2	1.2%
Germany	1	0.6%
Greece	2	1.2%
India	2	1.2%
Ireland	69	39.9%
Italy	5	2.9%
Japan	1	0.6%
Lithuania	1	0.6%
Malta	3	1.7%
Morocco	1	0.6%
The Netherlands	6	3.5%
New Zealand	3	1.7%
Poland	1	0.6%
Romania	1	0.6%
Saudia Arabia	1	0.6%
Singapore	1	0.6%
Spain	1	0.6%
Sweden	1	0.6%
USA	16	9.2%
Total	173	100.0%

Chapter 5

Table 5.3 List of GDM prevention and treatment outcomes carried forward from round 2 and their status following round three voting and discussion at the consensus meeting

Prevention Outcomes	Consensus following Round 3 vote	Consensus following meeting
1. Maternal Outcomes		
GDM Diagnosis	Consensus in	Consensus in
Gestational Weight Gain	Consensus in	Consensus in
Requirement for insulin therapy	Consensus in	Consensus out
Blood pressure	No consensus	Consensus out
Hypertensive disorders of pregnancy	Consensus in	Consensus in
Physical activity	No consensus	Consensus out
Fasting blood glucose	Consensus in	Consensus out
Postprandial glucose	Consensus in	Consensus out
Hba1c	Consensus in	Consensus out
2. Neonatal Outcomes		
Preterm birth	Consensus in	Consensus in
Gestational week at birth ^a	Consensus in	Consensus in
Neonatal death	Consensus in	Consensus in
Stillbirth	Consensus in	Consensus in
Small for gestational age	Consensus in	Consensus in
Large for gestational age	Consensus in	Consensus in
Macrosomia	Consensus in	Consensus out
Birthweight	Consensus in	Consensus in
Congenital malformation	No consensus	Consensus out
Brachial plexus injury	No consensus	Consensus out
Shoulder dystocia	Consensus in	Consensus out
Neonatal hypoglycemia	Consensus in	Consensus in
Admission to neonatal ICU	Consensus in	Consensus out
Treatment Outcomes		
1. Maternal Outcomes		
Adherence to the intervention	Consensus in	Consensus in
Glucose fasting	Consensus in	Consensus out
1 hour glucose tolerance test result	Consensus in	Consensus out
2 hour glucose tolerance test result	Consensus in	Consensus out
Hypertensive disorders of pregnancy	Consensus in	Consensus in
Requirement for insulin	Consensus in	Consensus out
Gestational age at insulin therapy	Consensus in	Consensus out
Total daily insulin dose	No consensus	Consensus out
Requirement for pharmacological therapy for hyperglycaemia ^b	Consensus in	Consensus in

Chapter 5

Gestational weight gain	Consensus in	Consensus in
Birth complication	Consensus in	Consensus out
Mode of birth	Consensus in	Consensus in
Reason for caesarean birth	No consensus	Consensus out
Maternal mortality	Consensus in	Consensus out
Maternal serious morbidity	Consensus in	Consensus out
Development of type 2 diabetes	Consensus in	Consensus out
2. Neonatal Outcomes		
Macrosomia	Consensus in	Consensus out
Birthweight	Consensus in	Consensus in
Large for gestational age	Consensus in	Consensus in
Small for gestational age	Consensus in	Consensus in
Gestational age at birth	Consensus in	Consensus in
Preterm birth	Consensus in	Consensus in
Shoulder dystocia	Consensus in	Consensus out
Neonatal mortality ^c	Consensus in	Consensus in
Neonatal hypoglycaemia	Consensus in	Consensus in
Need for IV glucose	Consensus in	Consensus out
Neonatal intensive care unit admission	Consensus in	Consensus out
Livebirth	Consensus in	Consensus out
Stillbirth	Consensus in	Consensus in
Perinatal death	Consensus in	Consensus out

^arephrased at consensus meeting to “gestational age at birth”

^brephrased at consensus meeting to “requirement and type of pharmacological therapy”

^crephrased at consensus meeting to “neonatal death”.

Chapter 5

Table 5.4 Final COS to be included in future GDM prevention and treatment research

Domain	Outcome
Maternal outcomes	<ol style="list-style-type: none">1. GDM diagnosis^a2. Adherence to the intervention3. Hypertensive disorders of pregnancy4. Requirement and type of pharmacological therapy for hyperglycaemia5. Gestational weight gain6. Mode of birth
Neonatal outcomes	<ol style="list-style-type: none">1. Birthweight2. Large for gestational age3. Small for gestational age4. Gestational age at birth5. Preterm birth6. Neonatal hypoglycaemia7. Neonatal death8. Stillbirth

^aRelevant to GDM prevention studies only

5.2.5 Discussion

In this study, a global group of key stakeholders agreed on 14 outcomes to form a COS essential for future trials of GDM prevention or treatment (Table 5.4). These outcomes are grouped under two domains including six maternal and eight neonatal outcomes. Although the COS was developed with a specific focus on randomised trials, it should be useful for non-randomised studies and audit in this field¹⁸⁶. It is anticipated that this COS will improve consistency in outcome reporting, facilitate data synthesis and increase the quality of research relevant to GDM prevention and treatment. The formation of this COS responds to previous calls for the development of a COS in this area to reduce research waste and improve health outcomes for women with GDM¹⁹⁰. The COMET handbook¹⁸⁹ and the Core Outcome Set–Standards for Development (COS-STAD)¹⁸⁸ were used to guide the development of this study and a detailed protocol was published. The three-step approach involving a systematic review, e-Delphi survey and consensus meeting has been used widely in COS development^{85, 88, 92}. Given the extensive body of published literature in the area of GDM prevention and treatment,

Chapter 5

the study team used sequential searching with relatively narrow time limits until outcome saturation was reached. It was believed that an exhaustive search of previously reported trials with no time limit would require extensive resources and would likely be of low yield. This pragmatic method yielded a comprehensive list with a total of 190 outcomes available for rating in round 1 of the e-Delphi study. In this next step of the study, a large and international group of stakeholders prioritised the identified outcomes. This method allows participants to have an equal voice in rating and to suggest additional outcomes for consideration in the next round of the e-Delphi. Participants were limited to submitting two additional GDM prevention and two additional GDM treatment outcomes; additional outcomes were carried forward only if suggested by more than one stakeholder. Based on prior experience, additional outcomes are very unlikely to be included in the final COS if suggested by just one person and we wished to avoid survey fatigue by extending an already long survey^{85, 88}.

The consensus meeting brought together a diverse group including women representatives, researchers and clinicians of varying backgrounds. A broad range of viewpoints was heard and the chairperson facilitated this. Special attention was taken to ensure that women representatives were given the opportunity to take part actively and plain language explanations were provided for each outcome under discussion. Two healthcare professionals were charged with providing further explanations on outcomes particularly to women representatives. This seemed to enhance the participation of the women representatives. The use of an anonymous voting system prevented participants feeling pressurised into voting a specific way following the group discussion. During the meeting, the women representatives shared many personal experiences in order to highlight the real-life impact of a specific outcome, and this was valued within the group.

The systematic review was limited to English language publications. This may have introduced a selection bias, although given the large number of included studies from a variety of centres internationally the likelihood of missing important outcomes is low. We did not introduce a qualitative aspect to the first phase of the study, such as semi-structured interviews. It may be argued that this could minimise patient involvement and the number of patient-centred outcomes included in the e-Delphi study. However, women representatives were included at every stage of the study and were active participants in the core study group, the study advisory group, the e-Delphi process (with the opportunity to add additional outcomes) and the consensus meeting. In addition, outcomes were only excluded during the e-Delphi stage if

Chapter 5

≤50% participants scored them as 7–9 in each of the stakeholder groups. This resulted in more outcomes being brought forward to the consensus meeting but gave stakeholder representatives the opportunity to explain their rationale for marking an outcome highly.

We adapted a snowball sampling approach for the e-Delphi study. This allowed participants to recruit additional participants but meant that we did not know how many potential participants actually responded to the survey. However, we did exceed our specified goal of at least 20 respondents from each stakeholder group in round 1⁸⁹ and the retention rates of 70% between rounds 1 and 2 and 84% between rounds 2 and 3 compare well to prior COS studies^{85, 185}. The greatest non-response rate to rounds 2 and 3 were among healthcare professionals. Interestingly, this group had formed the majority of participants in round 1. The implications of this with respect to the final COS is unclear, although we are reassured that this group still had significant representation at each point in the study. While study participants had a broad range of backgrounds and countries of residence, developing countries were not well represented. This may limit generalisability of the study to these areas of the world and future work should explore this issue in more detail. Finally, the scope of this study was to identify ‘what’ and not ‘how’ outcomes should be collected. There is a published repository of acceptable definitions relating to diabetes in pregnancy outcomes that may be referenced by researchers in order to define ‘how’ outcomes can be collected⁶⁵.

The issue of presenting one COS applicable to both GDM prevention and treatment studies was discussed in detail at the face-to-face meeting and a final decision was based on an electronic vote that was unanimous in favour of combining. This approach was recently taken by COSGROVE study researchers who developed a COS for prevention and treatment of fetal growth restriction¹⁸⁵. The next important step will be to ensure effective dissemination and uptake of the COS and it was the group consensus that having one COS, rather than two, would facilitate this process.

In summary, this is the first study to define a COS in the area of GDM prevention and treatment. It is anticipated that these outcomes, considered essential by key stakeholders, are collected in future trials and will have a positive impact on the ability to compare and combine studies. This will allow better assessment of the effect of a specific intervention, particularly in relation to rare but important outcomes (such as stillbirth and neonatal death), that individual studies may not be adequately powered to assess. The authors now call on funders, researchers

Chapter 5

and journals to incorporate this COS into relevant studies with the aim of improving research in the field of GDM and ultimately outcomes for women with GDM and their offspring.

Chapter 5

5.3 Paper 5: Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review

*Egan AM, Bogdanet D, Biesty L, **Kgosidialwa O**, McDonagh C, O'Shea C, O'Shea PM, Devane D, Dunne FP; INSPIRED research group. Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review. Diabetes Care. 2020 Dec;43(12):3129-3135. [https://doi:10.2337/dc20-1621](https://doi.org/10.2337/dc20-1621).*

Chapter 5

5.3.1 Abstract

Core Outcome Sets (COS) contain an agreed minimum set of outcomes to be measured and reported in all studies in a specific area, with the objective of standardizing outcome reporting. COS may minimize research waste by identifying outcomes important to key stakeholders, allowing for improved evidence synthesis, and facilitating translation of research findings to clinical practice. Over the past 5 years, there has been significant progress in developing COS relevant to studies of diabetes in pregnancy. This review summarizes work in this area, reviews the role of patient and public involvement in COS development, and suggests areas for future research.

5.3.2 Core Outcome Sets: Background and Rationale

Worldwide estimates suggest that hyperglycemia in pregnancy affects 21 million live births annually¹⁷². Approximately 85% of these are due to gestational diabetes mellitus (GDM) with the remainder a result of pre-existing maternal diabetes¹⁹¹. Diabetes poses an increased risk of multiple adverse outcomes for both mother and baby during and after pregnancy. In 1989, the St Vincent Declaration set a 5-year target for approximating outcomes of pregnancies in women with diabetes to those of the background population²⁸. While these goals have not been reached, the past 30 years have witnessed an intensive research effort to improve outcomes for women with diabetes and their children.

When designing a clinical trial, and indeed any research study, researchers must decide which outcomes to measure and report. Multiple factors influence this decision including responsiveness of the outcome to the intervention, cost of measuring an outcome, and acceptability and importance of an outcome to study participants¹⁸⁹. Outcomes reported from diabetes in pregnancy studies differ widely, and this lack of consistency makes meaningful comparisons between studies difficult⁸⁵. It also limits our understanding of intervention effects. For example, a systematic review and meta-analysis of 21 studies of pre-pregnancy care (PPC) for women with pre-gestational diabetes noted that just 13 studies included congenital malformations as an outcome and only 5 included changes in the level of glycated hemoglobin (HbA1c)¹⁹². Reporting bias is an additional concern within scientific literature as a whole. Studies with positive results are more likely to be published, and a review of cohort studies assessing outcome reporting bias in randomized controlled trials demonstrated that 40–62% of studies had at least one primary outcome changed, introduced, or omitted¹⁹³. Finally, there is concern that selected outcomes do not always reflect the values and preferences of study

Chapter 5

participants, who are key stakeholders in development and assessment of clinical interventions. For example, a study on dietary advice for GDM management found that stress and anxiety were reported as important outcomes from the woman's perspective. Still, these are reported rarely in existing GDM-management literature¹⁹⁴.

In an attempt to overcome these issues, there is a move to develop core outcome sets (COS) in the field of diabetes and pregnancy and other areas of research and clinical practice. A COS is the minimum set of outcomes or outcome measures and is a consensus-driven recommendation of "what" should be measured and reported in all studies for a given health issue¹⁸⁹. In addition, there is the recognition that COS are also important in informing decisions about outcomes to be recorded in routine clinical data and for clinical audit/quality improvement projects. Of course, the aim of a COS is not to curb innovation, and so researchers are free to measure and report additional outcomes of interest. Due to sample size and cost limitations, it is not expected that individual studies are powered to examine differences in all specified outcomes within a COS; however, measurement of the components will facilitate future combining and comparing of multiple studies within a field of research. The Core Outcome Measures in Effectiveness Trials (COMET) initiative brings together people interested in the development and application of such outcome sets. It has developed a handbook and additional reference material that provide detailed guidance on COS development^{186, 189}. The concept of standardizing outcomes is not novel. In the 1970s, the World Health Organization led a collaboration resulting in the World Health Organization handbook of guidelines recommending the minimum requirements for data collection in cancer trials¹⁹⁵. More recently, the Outcome Measures in Rheumatology (OMERACT) collaboration has driven the development of COS in rheumatoid arthritis and other rheumatic diseases¹⁹⁶. To streamline COS development, the Core Outcome Set–STAndards for Development (COS-STAD)¹⁸⁸ provides minimum standards to be followed by COS developers and the Core Outcome Set–STAndardized Protocol items (COS-STAP) consists of a checklist of 13 items considered essential documentation in a COS protocol⁶⁹. The Core Outcome Set–STAndards for Reporting (COS-STAR) statement is a helpful resource to standardize COS reporting⁷⁰.

This review summarizes completed and ongoing COS development in the area of diabetes in pregnancy, reviews the role of patient and public involvement (PPI) in COS development, and discusses opportunities for future progress in this area.

Chapter 5

5.3.3. Methods

The PubMed database and COMET registry (www.comet-initiative.org) were searched for English-language studies and COS publications. The following search terms were used alone and in combination: “diabetes,” “pregnancy,” “COS,” and “core outcome set.” A date restriction was not applied. Results were reviewed by the authors and selected for inclusion based on relevance to the topic. Additional articles were identified by manual searching of reference lists of included articles. The patient perspective was provided by co-authors (CM and CO) who have experience as patient and public representatives in COS development as part of the INternational collaboration for Studies in PREgnancy and Diabetes (INSPIRED) research group. The information was obtained from their written responses to open-ended questions reflecting their experience as COS developers.

5.3.4 COS in Diabetes in Pregnancy: Existing Work

In 2012, Bennett et al.¹⁸² used a systematic review with stakeholder input to identify clinically important research questions and high-priority outcomes for the management of GDM. This review was one of the first attempts to address outcome reporting in this field. Acknowledging that waste in research may result from important outcomes not being measured or reported in clinical trials and reviews in Australia, the WOMen and Babies health and wellbeing: Action through Trials (WOMBAT) Collaboration recognized a critical need to standardize outcomes. Following review and consensus discussion, the group developed and disseminated a useful list of standardized outcomes for GDM. Bain, Middleton, and Crowther¹⁹⁰ examined the use of these GDM outcomes in Cochrane protocols and reviews before and after the publication of the WOMBAT outcomes list. The authors found an increase in the number of prespecified outcomes reported over time in Cochrane reviews attributed to the WOMBAT initiative. The authors emphasized a need to move further toward an international COS for GDM research.

In 2014, recognizing that variation in outcome collection and reporting is a serious hindrance to progress in the specialty of women’s and newborn health, >80 journals came together to endorse the CoRe Outcomes in Women’s and Newborn health (CROWN) initiative¹⁸⁷. As a consortium, CROWN encourages the development of COS using robust consensus methodology and aims to organize robust peer-review and effective dissemination of manuscripts describing COS. It is hoped that this approach will facilitate the embedding of COS in research practice and encourage close collaboration between researchers, reviewers, funders, and guideline makers.

Chapter 5

Following this call for action, three COSs have been published in the field of diabetes in pregnancy by the INSPIRED research group. This group comprises researchers, health care professionals, and patient representatives from a broad geographical base, including representatives from low-/middle-income countries, who work together in a committed way to improve research in this field. Recruitment to the research group has taken place by raising of awareness at international meetings and within special interest groups by e-mails to the chairpersons and individual members where possible. Thus far, the group has had an open-door policy to membership and welcomes new and interested stakeholders. Their published COS focus on studies evaluating the effectiveness of PPC for women with pre-gestational diabetes^{85, 87}, follow-up at 1 year and beyond of women with GDM treated with insulin or oral glucose-lowering agents^{88, 166}, and studies of GDM prevention and treatment^{89, 197}. The INSPIRED research group is currently developing a COS for studies of treatments for women with pre-gestational diabetes, and a study protocol on the development of a COS for diabetes after pregnancy prevention interventions (COS-DAP) has been published by another international group of researchers^{198, 199}. Table 1 outlines these completed and ongoing studies.

Chapter 5

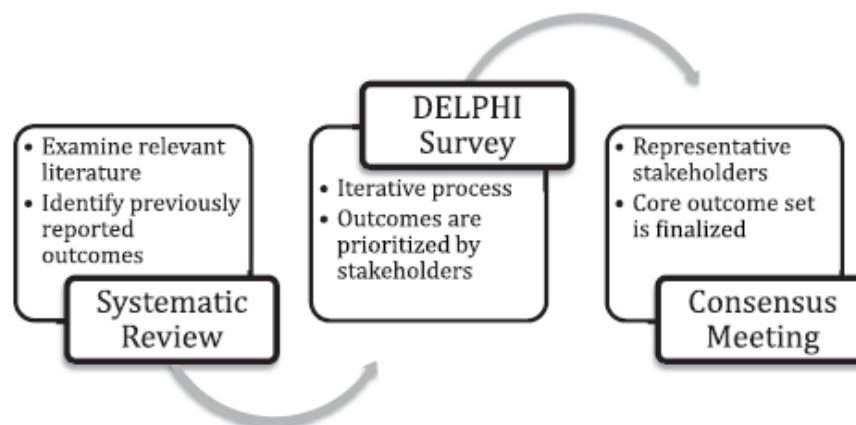
Table 5.5 Summary of COS publications relevant to diabetes in pregnancy

Article title	A Core Outcome Set for Studies Evaluating the Effectiveness of Prepregnancy Care for Women With Pregestational Diabetes	Follow-up at 1 Year and Beyond of Women With Gestational Diabetes Treated With Insulin and/or Oral Glucose-Lowering Agents: A Core Outcome Set Using a Delphi Survey	Development of a Core Outcome Set for Diabetes After Pregnancy Prevention Interventions (COS-DAP): A Study Protocol	A Core Outcome Set for Studies of Gestational Diabetes Mellitus Prevention and Treatment
Citation	Diabetologia 2017;60:1190–1196	Diabetologia 2019;62:2007–2016	Trials 2018;19:708	Diabetologia 2020;63:1120–1127
Databases searched	MEDLINE, EMBASE, Web of Science, CENTRAL, CINAHL, ClinicalTrials.gov	MEDLINE, EMBASE, Web of Science, CENTRAL, CINAHL, ClinicalTrials.gov	MEDLINE, EMBASE, OVID, CINAHL, CENTRAL, Cochrane Pregnancy and Childbirth's Trials Register	MEDLINE, EMBASE, Web of Science, CENTRAL, CINAHL, ClinicalTrials.gov
Search limitations	English language, no time limitation, prospective cohort studies, case-control studies, RCT, and systematic reviews	English language, no time limitation, RCT, and RCT follow-up studies	English language, no time limitation, RCT, pre- and postintervention studies, multicenter studies, clinical trials, comparative studies, evaluation studies, and intervention protocols	English language, RCT and systematic reviews of randomized trials, time restricted until outcome saturation
Systematic review summary	1,127 abstracts identified, 33 articles for final review, 86 outcomes for the Delphi study	3,344 abstracts identified, 25 articles for final review, 121 outcomes for the Delphi study	N/A	929 abstracts identified, 135 articles for final review, 74 GDM prevention outcomes, and 116 GDM treatment outcomes for the Delphi study
Delphi study	Round 1, 151 respondents; round 2, 120 respondents; round 3, 101 respondents	Round 1, 288 respondents; round 2, 190 respondents; round 3, 165 respondents	N/A	Round 1, 173 respondents; round 2, 121 respondents; round 3, 102 respondents
Delphi survey international participation	24 countries, 5 continents	33 countries, 5 continents		27 countries, 6 continents
Patient and public involvement	Yes	Yes	Yes	Yes
Consensus meeting	Yes	Yes	Yes	Yes
Final consensus	17 outcomes	9 outcomes	N/A	14 outcomes

CENTRAL, Cochrane Central Register of Controlled Trials; N/A, not available; RCT, randomized controlled trial.

While there are a variety of approaches to COS development, the studies in Table 5.5 have followed a process involving three distinct steps (Figure 5.4), as follows.

Figure 5.4 Typical steps toward COS development



Chapter 5

1) A Systematic Review to Identify Previously Reported Outcomes

This generally involves a standard approach with multiple database searches and minimal time limits to generate a long list of outcomes. However, in specific disease areas, the task of examining all previous literature may be overwhelming and require intensive use of resources. One pragmatic approach to overcoming this while also capturing the majority of outcomes is to conduct the systematic review in stages defined by year of publication until outcome saturation is reached^{86, 189}.

2) Prioritization of Previously Reported Outcomes and Inclusion of Additional Outcomes Suggested by Key Stakeholders

Delphi surveys are used frequently during this step. This iterative method was developed at the Rand Corporation in the 1950s and aims to achieve convergence of opinion in sequential questionnaires sent by post or electronically¹⁸⁹. Typically, participants are asked to rate the importance of including each outcome in the COS on a Likert scale with an option to suggest additional outcomes that are not listed. Participants then have the opportunity to consider the views of other participants before rerating each item on subsequent surveys (typically two or three rounds in total). After the initial survey round, some items may be dropped according to prespecified criteria⁸⁶.

3) A Consensus Meeting to Decide on the Final COS

This is traditionally a face-to-face meeting where stakeholder representatives discuss the survey results and vote on each outcome for inclusion in the COS. Again, prespecified criteria should be used to structure the meeting and define consensus. An experienced facilitator is essential to ensure that all parties are included in the discussion and that there is adherence to the prespecified approach in achieving consensus⁸⁶. The feasibility and potential barriers to measuring each outcome should be discussed. This will improve the future implementation of the final COS.

5.3.5 Key Stakeholders: The Role of PPI

Key to successful COS development is identifying and involving key stakeholders. Ideally, participants will represent all key stakeholders and commonly include health care practitioners, trialists, researchers, and policy makers. However, the expertise of patients and carers in development of COS is critical and well recognized¹⁶⁸. Indeed, the outcomes on which research

Chapter 5

studies report should be important and relevant to those who will potentially receive care based on the findings. The guidance offered by the COMET initiative and included in the COS-STAD recommendations highlights the contribution patients and their families/carers can make in COS development^{70, 189}. This contribution typically presents as follows:

- 1) PPI as part of the research team involved in planning/designing and conducting the study and
- 2) Patient and public stakeholders in the study as research participants.

The distinction between involvement and participation is not always explicit in published reports of COS¹⁶⁸; however, both warrant consideration in future studies including those within the context of diabetes in pregnancy.

PPI in the context of point 1 (noted above) relates to the inclusion of “public research partners” and is underpinned by the definition offered by INVOLVE (a U.K. national advisory group to support active public involvement in research) that research is carried out “with/by” rather than “for/about” members of the public²⁰⁰. The COMET initiative suggests that PPI can facilitate this by their presence on the Study Advisory Group¹⁸⁹. Such involvement ensures that the voices of patients and the public contribute to the focus and design of the study, provide input at each stage of the research process, and are part of the dissemination strategy¹⁶⁸. PPI can, and should, bring insight into methods for the design, conduct, and reporting. As the methodology of COS development has advanced, the inclusion of patients and the public as research participants has also increased²⁰¹. In its broadest sense, this is viewed as a means to ensure that outcomes important to patients are included in the COS²⁰². While the best approaches for facilitating patient inclusion are as yet unknown¹⁶⁸, guidance is offered by the COMET initiative and by participants and researchers of previous COS studies^{168, 202-204}.

It is acknowledged that the systematic review approach typically used in the first stage of COS development could lend itself to identifying outcomes that are important to researchers only¹⁶⁸. Qualitative research, using data collection methods of individual and/or focus group interviews, can enhance this stage by identifying outcomes that are important to patients and the public and therefore include the wider stakeholder community²⁰³. In-depth exploration using qualitative research techniques may help uncover outcomes engrained within the experiences of patients that might otherwise be missed. Qualitative approaches can also give insight into why some outcomes are considered more important than others to specific stakeholder groups²⁰⁵. Delphi

Chapter 5

surveys have been identified as the most commonly used way to ensure patient and public participation in COS development²⁰².

Published COS studies of diabetes in pregnancy have used this method whereby health care professionals, researchers, and women (with a history of diabetes) have participated across the Delphi rounds^{85, 86, 166}. Researchers are cautioned, not without its challenges, to ensure that outcomes are presented in a way that is accessible to all groups (e.g., plain language descriptions are usually required for all groups and not just for stakeholders without a clinical background)²⁰¹. The final stage of COS studies involves a consensus meeting to agree on the final list of outcomes.

COMET initiative notes that some consensus meetings include all stakeholders, while others may run a separate meeting for the patient and public participants¹⁸⁹. The published COS for studies of diabetes in pregnancy facilitated all stakeholder groups, including representatives of women with diabetes, within one consensus meeting^{85, 86, 166}. Bringing all participants to the discussion gave perspective on what was held as important to all groups¹⁶⁶. Table 5.6 outlines key sentiments of two of our co-authors: women with diabetes who have experience in COS development and self-managing diabetes during pregnancy. Overall, they described a positive experience and recognized the value of their contributions. However, these women were selected based on their prior experience and involvement with COS development and may not represent all women with diabetes, particularly from a cultural perspective. Further exploration of the public and patient's experiences of participating in COS development is warranted. A working group (People and Patient Participation, Involvement and Engagement [PoPPIE]) established within the COMET initiative focuses specifically on the public's involvement and participation in the development of COS. Future COS work, including studies of diabetes in pregnancy, should ensure that methods supporting involvement and participation are sustainable, meaningful, and evaluated robustly. We also suggest that COS publications include a tailored PPI statement describing the PPI involvement including at what stage in the study the patients/public first became involved and how their concerns and preferences informed the developed outcome measures.

Chapter 5

Table 5.6 PPI in COS development: written feedback from representatives

"I have been involved in a number of COS and the experience has been eye-opening."
"It was a pleasure and a privilege to work with the team."
"Core outcome set research is so important to myself and all women with diabetes."
"It is important that patients are involved in research studies because essentially the research is about their condition and they know their condition best."
"It is vital that researchers know what outcomes are most important to patients—it may be different to what a health care professional believes is important."
"I felt that my opinion was valued by the team at every step of the process."
"I would recommend participation to other patients because I believe that broader participation can lead to better outcomes."
"I would be happy to be involved in future studies and help progress diabetes care."

5.3.6 Defining Priority Areas for COS Development

As COS development progresses, it is important to identify and prioritize areas within the field of diabetes and pregnancy requiring COS and explore how best to address this need. OMERACT has established working groups for subspecialty areas in rheumatology where members work virtually and meet at a biennial conference¹⁹⁶. There is not a similar working group for diabetes and pregnancy, but the James Lind Alliance Priority Setting Partnerships were established in 2019 to identify areas for research to improve the health and wellbeing of mothers, babies, and families affected by diabetes in pregnancy²⁰⁶. They have produced a top 10 list of research questions that women, their support networks, and health care professionals agree are the most important for research to address in diabetes and pregnancy¹⁵⁶. There is potential for COS developers to establish a working relationship with the James Lind Alliance and bring together patients, carers, and clinicians.

5.3.7 Scope and Representativeness of COS

Defining the scope of each COS is important and should be clarified during COS protocol development. When developing lists of previously reported outcomes using systematic review methodology, COS developers typically include randomized trials or systematic reviews of randomized trials^{88, 89}. However, in areas where randomized trials are limited, the systematic review has included additional study designs such as prospective cohort studies and case control trials⁸⁷. This raises the question of whether a COS is relevant to all study types in a specific area. For example, will a COS be relevant to basic science as well as clinically focused studies in a specific field? We would argue that, if available, an appropriate COS should be

Chapter 5

used for all forms of research. Ideally, COS developers will present a list of study types that might be within the purview of the COS at the time of publication; however, study designers will ultimately need to judge whether a published COS applies to their particular research question(s).

The global applicability of any particular COS is currently unclear. In particular, developing countries are often heavily underrepresented during COS development and the geographical distribution of participants in any specific COS is usually focused around certain regions⁸⁵. This may be related to lack of resources (both time and financial) needed to participate in the process or a perception that the final product will not be relevant to their research or clinical practice. Strategies such as translating surveys into different languages and having a facilitator engage with stakeholders during the Delphi process could be helpful but have not been evaluated. Relating to this point, international guidelines can recommend different approaches to diagnosis and management of a particular condition depending on available resources and infrastructure, even if not supported by high-quality evidence. This is the case for GDM and is based on the premise that some structured care is preferable to no care at all²⁰⁷. With this in mind, it may be necessary to develop different COS (or COS modifications) for different clinical settings. While further guidance is awaited, there is an onus on COS developers to consider the practicality and cost when recommending an outcome for inclusion in a COS.

It is worth noting that COS studies are designed typically to identify “which” outcomes are important to measure not necessarily “how” to measure these outcomes. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) Working Group on Outcome Definitions has already published a repository of definitions that is a handy resource for researchers once the core outcomes have been selected⁶⁵. This repository includes both maternal and fetal outcome definitions and was assembled using a thorough systematic review to identify previously reported definitions, followed by an expert review to ensure accuracy. Unfortunately, there is not yet an international consensus on the best approach to diagnose GDM, which is responsible for the majority of cases of diabetes in pregnancy.

5.7.8 Methodological Advances and Review of Existing COS

Newer techniques such as real-time Delphi offer potential “round-less” approaches to achieving consensus but have yet to be explored comprehensively in COS development²⁰⁸. This method encourages respondents to revisit an online questionnaire as often as they want within

Chapter 5

a specified time frame. Participants can see their responses as well as the updated answers of others. This has the potential to allow for dialogue between respondents and reach consensus in a more time-efficient manner. This automated approach could significantly reduce facilitator burden, but issues such as maintaining stakeholder engagement throughout the process need to be examined. It will be necessary to formally evaluate real-time Delphi against the more traditional approach to assess what, if any, differences exist.

Digital communication technologies have rapidly advanced in the past decade, and the coronavirus disease 2019 pandemic has witnessed a surge in their use both within and outside of the workplace. In the face of adversity, the medical community has adapted significantly to facilitate ongoing research, education, and patient care in this new era of social distancing and shelter-in-place orders. Our increased familiarity with teleconferencing platforms and etiquette can be used to broaden the geographical base and make it easier for stakeholders (including PPI) from a range of low- to high-income countries to actively participate in COS development. For example, it now seems reasonable to consider replacing the traditional face-to-face consensus meeting with an online gathering as is anticipated with an ongoing COS¹⁹⁹. This approach has the potential to save time and money, and sessions can be easily archived for future review. Removing the cost and time associated with traveling may allow greater participation from those in lower-income and geographically distant countries. Supported by an experienced facilitator and using electronic polling methods, a technology-enabled meeting may result in less peer pressure between participants and a more inclusive COS.

Another area of debate is how frequently a COS should be revised. Periodic review will allow developers to confirm the ongoing relevance of the COS by ensuring all outcomes are still important and that no additional outcomes should be added. Perhaps this periodic review could be the responsibility of a lead group who would perform this task on behalf of all diabetes in pregnancy stakeholders. For example, the International Headache Society Committee on Clinical Trials published guidelines for studies of pharmacological treatments for tension headaches in 1995²⁰⁹. They specified that a revised guideline was planned for 3–4 years from that date, and although additional time lapsed, an updated report was published in 2010²¹⁰. The potential of a “living COS,” where the COS is updated continually as new, relevant evidence becomes available, should also be explored. This is already being done in the systematic review field whereby living systematic reviews are underpinned by continual monitoring of the evidence; the inclusion of new, relevant evidence; and a process for communicating the up-to-

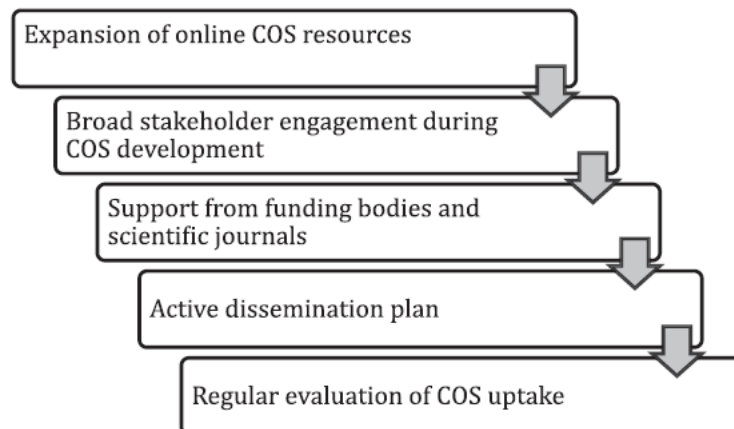
Chapter 5

date status of the review. Outcomes in the COS will likely be more temporally stable than data informing living systematic reviews. Nevertheless, the processes for omitting already included outcomes and including new outcomes in a living COS require careful thought.

5.7.9 COS Dissemination and Uptake

COS developers have an opportunity, and arguably a responsibility, to galvanize COS implementation and disseminate knowledge of the utility of COS and their potential value for future research. This has been achieved in other areas of health care where COS development is more established. For example, >80% of relevant clinical trials now use the rheumatoid arthritis COS²¹¹. Prior work has solicited and evaluated dissemination ideas from COS research participants and listed strategies to improve the relevance, usefulness, and comparability of outcomes in clinical practice^{212, 213}. Drawing on this information, we propose the following roadmap for COS implementation in the field of diabetes in pregnancy (Figure 5.5).

Figure 5.5 Road map for COS implementation in the field of diabetes in pregnancy



COS Core outcome set

Expansion of Online COS Resources

Prospective online registration of a planned COS with COMET is an important first step for all COS developers¹⁹⁹. We recommend expansion of the currently available online COS resources to include formal training programs for researchers, health care professionals, and patient representatives. This will raise awareness of the role of COS and COS methodology and facilitate a quality framework around COS development.

Chapter 5

Broad Stakeholder Engagement During COS Development

During COS development, stakeholder representation should be as inclusive as possible from the time of study conception. Consideration should be given to inviting representatives from key scientific journals, funding bodies, special interest groups, societies, and national health departments. For example, although members of the INSPIRED research group are also members of key diabetes and pregnancy organizations, achieving formal endorsement would almost certainly increase engagement with COS development and downstream use of the final product.

Support from Funding Bodies and Scientific Journals

Progress has clearly occurred in this regard with major funders such as the National Institute for Health Research in the U.K. and the Health Research Board in Ireland highlighting the importance of, and need for, COS to researchers seeking funding for new trials¹⁸⁹. In the U.S., the National Institutes of Health encourages the use of common data elements in clinical research, patient registries, and other human subject research with the aim of improving data quality and synthesis²¹⁴. A data element is information that describes a piece of data to be collected in a study, and so this concept is broadly similar to a COS, although COS are largely outcome-only focused. An increase in uptake of the rheumatoid arthritis COS was noted after its endorsement by the U.S. Food and Drug Administration in 1996 and the European Medicines Agency in 1998²¹⁵. We propose that major funders take the additional step of insisting that grant reviewers ask authors whether a COS relevant to their study was available and whether it was used to identify and measure study outcomes. The response should be taken into account in judging of the submitted work. Similarly, while a large number of journals in the field of women's health support COS development through the CROWN initiative, we suggest including information on COS in their "instructions for authors" web page and specifically asking authors during the submission process whether a relevant COS was used.

Active Dissemination Plans

The approach to achieving widespread dissemination of a completed COS should be carefully considered. Along with traditional methods such as presenting at scientific conferences and publishing the COS in a high-impact journal, researchers should also consider the role of social media outlets and other online platforms in their approach. Indeed, electronic modes of dissemination including social media efforts and e-mails to stakeholders and professional

Chapter 5

groups are associated with an increase in COS stakeholder interest²¹². COS developers can take the lead in informing research funders in the area of health or social care, guideline producers, and Cochrane review groups on completion of a relevant COS¹⁸⁹.

Evaluation of COS Uptake

The uptake of an individual COS should be assessed regularly. With this strategy, the impact of specific dissemination activities can be evaluated and barriers to dissemination and uptake can be examined and addressed. This approach can also yield unexpected information requiring further exploration. For example, it has recently been noted that commercially funded trials are more likely to measure the rheumatoid arthritis COS outcomes compared with those without industry funding²¹².

5.7.10 Summary

COS are a means to facilitate research in a particular area of health care that will address outcomes of importance to key stakeholders. Using a COS does not limit researchers from collecting additional outcomes of interest and relevance to their study. COS development has progressed in the field of diabetes in pregnancy and has the potential to reduce heterogeneity between trials and improve reporting. This should translate into improved evidence synthesis and knowledge transfer to reduce research waste, better inform clinical practice, and result in improved pregnancy outcomes for women with diabetes.

Chapter 6

Chapter 6: Discussion and Conclusions

Chapter Introduction

This final chapter presents an overview of the thesis. Pre-gestational diabetes (PGDM) is one of the most common chronic illnesses complicating pregnancy. T1DM and T2DM are the commonest forms of pre-existing diabetes affecting pregnancy. The incidence of PGDM continues to increase globally with significant healthcare and economic burden. As a result, the research community continues to intensify its effort to improve outcomes for both mother and baby affected by PGDM in the form of PPC, pharmacology, technology and education. It is evident however that evidence synthesis in this field of maternal diabetes is hampered by outcome reporting heterogeneity.

In the area of maternal diabetes, outcome reporting heterogeneity has been recognised as a contributing factor to difficulties in evidence synthesis. As a result, the diabetes in pregnancy research community through the CROWN initiative made a call to the wider diabetes in pregnancy community to harmonise outcome reporting in women's health research⁷¹. The aim of this thesis was to develop a COS for future studies assessing treatment interventions in pregnant women with PGDM in order to build evidence and reduce research waste in this topic.

Chapter 2

Kgosidialwa O, Bogdanet D, Egan A, O'Shea PM, Biesty L, Devane D, Dunne F; INSPIRED group. Developing a core outcome set for the treatment of pregnant women with pregestational diabetes-a study protocol. Trials. 2020 Dec 11;21(1):1017. <https://doi.org/10.1186/s13063-020-04910-1>.

In this chapter the methodology for creating a COS in treatment interventions of pregnant women with PGDM is detailed.

Chapter 3

Kgosidialwa O, Bogdanet D, Egan A, Newman C, O'Shea PM, Biesty L, McDonagh C, O'Shea C, Devane D, Dunne F; INSPIRED group. A Systematic Review on Outcome Reporting In Randomised Controlled Trials Assessing Treatment Interventions in Pregnant Women with Pregestational Diabetes. BJOG. 2021. <https://doi.org/10.1111/1471-0528.16842>.

The systematic review of this thesis identified 67 RCTs assessing treatment interventions in pregnant women with PGDM. From these studies, 210 outcomes were extracted from the

Chapter 6

literature. One hundred and thirty-one outcomes (69 maternal, 61 neonatal/infant and one other) remained after the SAG removed duplicate outcomes and combined similar outcomes. There was significant diversity in outcome reporting (both ‘what’ and ‘how’) in this topic. Although some work has been done to address the ‘how’ to report outcomes⁶⁵ in the general field of diabetes in pregnancy, there is no guidance on ‘what’ outcomes to report in order to synthesise evidence on this topic. In this systematic review, although insulin and metformin were the most reported treatment interventions, there was significant variations in what outcomes were reported in each trial for each intervention. In addition, there was also differences in composite components in studies that reported on composite outcomes making comparisons between interventions difficult.

Chapter 4

Kgosidialwa O, Bogdanet D, Egan A, Newman C, O'Shea PM, Griffin TP, McDonagh C, O'Shea C, Carmody L, Cooray SD, Anastasiou E, Wender-Ozegowska E, Clarson C, Spadola A, Alvarado F, Noctor E, Dempsey G, Napoli A, Crowther C, Galjaard S, Loeken MR, Maresh MJA, Gillespie P, de Valk H, Agostini A, Biesty L, Devane D, Dunne F; INSPIRED group. A Core Outcome Set for The Treatment of Pregnant Women with Pregestational Diabetes: An International Consensus Study. BJOG. 2021. <https://doi.org/10.1111/1471-0528.16825>.

This thesis through robust methodology, identified a list of 19 (8 maternal and 11 fetal/infant) outcomes that are important to key international stakeholders including women with PGDM for inclusion into the COS.

This work also emphasised the importance of PPI in research. The systematic review revealed that women were rarely involved in research for them apart from being participants. In this thesis, women with diabetes were involved in key aspects of the study including as part of the SAG. Their input added insight into living with diabetes for researchers and clinicians.

This thesis was carried out during the COVID19 pandemic. Thus, in keeping with social distancing and other public health measures, the global consensus meeting was successfully carried out virtually where previous meetings were carried out face to face (discussed in chapter 5). Online communication could be used going forward particularly during the consensus meeting stage of COS development to encourage participation from low- to middle- income countries, and in so doing improve generalisability of the COS.

Chapter 6

Chapter 5

Egan, A.M., Bogdanet, D., Griffin, T.P., **Kgosidialwa O**, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. *Diabetologia* 63, 1120–1127 (2020). <https://doi.org/10.1007/s00125-020-05123-6>.

Egan AM, Bogdanet D, Biesty L, **Kgosidialwa O**, McDonagh C, O'Shea C, O'Shea PM, Devane D, Dunne FP; INSPIRED research group. Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review. *Diabetes Care*. 2020 Dec;43(12):3129-3135. <https://doi:10.2337/dc20-1621>.

In the first part of this chapter, a 14 outcome COS for studies of Gestational Diabetes Mellitus (GDM) prevention and treatment is presented. GDM is the most prevalent type of diabetes during pregnancy accounting for approximately 85% of diabetes cases in pregnancy¹⁹¹. In addition, the prevalence of GDM continues to rise globally mirroring that of obesity. As a result, for the past 30 years this area has witnessed an intensive research effort to improve outcomes for women with diabetes and their children. Unfortunately, evidence synthesis is hampered by variations in outcome reporting. Thus, this work aimed to develop COSs for studies evaluating the effectiveness of interventions for the prevention or treatment of GDM.

The systematic review identified 74 GDM prevention and 116 GDM treatment outcomes which were presented to key stakeholders in an eDelphi survey format to rank for inclusion into the COS. Upon completion of the consensus meeting involving key international stakeholders including women with GDM, 14 outcomes (6 maternal and 8 fetal/ infant) were identified for inclusion into the COS.

In the second part of this chapter, we review COSs for studies of diabetes in pregnancy. We discuss the history and aims of COSs, summarise current COSs in diabetes in pregnancy, review the role of PPI in COS development, and suggests areas for future research.

Future Directions

The James Lind Alliance through its Pregnancy Priority Setting Partnership (<https://www.npeu.ox.ac.uk/jla-ppsp>) has produced a top ten list of research questions that women with diabetes and their representative, researchers and healthcare providers agree are the most important for research to address in diabetes and pregnancy¹⁵⁶. This COS and those

Chapter 6

previously published by the INSPIRED group^{85, 86, 166} will be important to include in future research in order to synthesise robust evidence on the different interventions researched in PGDM and GDM. I hope that the (three) publication of the work presented in this thesis in high impact international journals will increase its visibility and uptake by the global community.

References

References

1. ADA. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27 Suppl 1:S5-S10.
2. WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. https://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_newpdf. 2006.
3. ADA. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15-S33.
4. WHO. Classification of diabetes mellitus. Geneva. Licence: CC BY-NC-SA 3.0 IGO. 2019.
5. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 2019;157:107843.
6. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37 Suppl 1:S81-90.
7. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health*. 2020;10(1):107-11.
8. Lowe WL, Jr., Scholtens DM, Kuang A, Linder B, Lawrence JM, Leberthal Y, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Gestational Diabetes Mellitus and Childhood Glucose Metabolism. *Diabetes Care*. 2019;42(3):372-80.
9. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ*. 2020;369:m1361.
10. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. *Diabet Med*. 2012;29(7):844-54.
11. Agarwal MM, Dhatt GS, Othman Y. Gestational diabetes: differences between the current international diagnostic criteria and implications of switching to IADPSG. *J Diabetes Complications*. 2015;29(4):544-9.
12. Misra S, Owen KR. Genetics of Monogenic Diabetes: Present Clinical Challenges. *Curr Diab Rep*. 2018;18(12):141.
13. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. *Endocr Rev*. 2008;29(3):265-91.
14. Maassen JA, LM TH, Van Essen E, Heine RJ, Nijpels G, Jahangir Tafrechi RS, et al. Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes*. 2004;53 Suppl 1:S103-9.
15. Deputy NP, Kim SY, Conrey EJ, Bullard KM. Prevalence and Changes in Preexisting Diabetes and Gestational Diabetes Among Women Who Had a Live Birth - United States, 2012-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(43):1201-7.
16. Wahabi H, Fayed A, Esmail S, Mamdouh H, Kotb R. Prevalence and Complications of Pregestational and Gestational Diabetes in Saudi Women: Analysis from Riyadh Mother and Baby Cohort Study (RAHMA). *Biomed Res Int*. 2017;2017:6878263.
17. Coton SJ, Nazareth I, Petersen I. A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. *BMJ Open*. 2016;6(1):e009494.
18. Peng TY, Ehrlich SF, Crites Y, Kitzmiller JL, Kuzniewicz MW, Hedderson MM, et al. Trends and racial and ethnic disparities in the prevalence of pregestational type 1 and type 2 diabetes in Northern California: 1996-2014. *Am J Obstet Gynecol*. 2017;216(2):177 e1- e8.
19. Illsley NP. Glucose transporters in the human placenta. *Placenta*. 2000;21(1):14-22.

References

20. Grasso S, Palumbo G, Rugolo S, Cianci A, Tumino G, Reitano G. Human fetal insulin secretion in response to maternal glucose and leucine administration. *Pediatr Res.* 1980;14(5):782-3.
21. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care.* 2007;30 Suppl 2:S112-9.
22. Buschur E, Stetson B, Barbour LA. Diabetes In Pregnancy. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. *Endotext.* South Dartmouth (MA)2000.
23. Pedersen J. Diabetes and pregnancy: Blood sugar of newborn infants (Ph.D. Thesis) Danish Science Press; Copenhagen. 1952 230.
24. Pedersen J. The pregnant diabetic and her newborn: Problems and management. William & Wilkins; Baltimore, MD. 1967:128–37.
25. Schwartz R, Gruppuso PA, Petzold K, Brambilla D, Hiilesmaa V, Teramo KA. Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. *Diabetes Care.* 1994;17(7):640-8.
26. Group HSCR, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991-2002.
27. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta.* 2015;36(7):709-15.
28. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med.* 1990;7(4):360.
29. Capobianco G, Gulotta A, Tupponi G, Dessole F, Pola M, Virdis G, et al. Materno-Fetal and Neonatal Complications of Diabetes in Pregnancy: A Retrospective Study. *J Clin Med.* 2020;9(9).
30. Fong A, Serra A, Herrero T, Pan D, Ogunyemi D. Pre-gestational versus gestational diabetes: a population based study on clinical and demographic differences. *J Diabetes Complications.* 2014;28(1):29-34.
31. Eidem I, Vangen S, Hanssen KF, Vollset SE, Henriksen T, Joner G, et al. Perinatal and infant mortality in term and preterm births among women with type 1 diabetes. *Diabetologia.* 2011;54(11):2771-8.
32. Idris N, Wong SF, Thomae M, Gardener G, McIntyre DH. Influence of polyhydramnios on perinatal outcome in pregestational diabetic pregnancies. *Ultrasound Obstet Gynecol.* 2010;36(3):338-43.
33. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. *Diabet Med.* 2010;27(4):431-5.
34. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sorensen HT, et al. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ.* 2019;367:l6398.
35. Fernandez-Twinn DS, Hjort L, Novakovic B, Ozanne SE, Saffery R. Intrauterine programming of obesity and type 2 diabetes. *Diabetologia.* 2019;62(10):1789-801.
36. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes.* 2000;49(12):2208-11.
37. Adane AA, Mishra GD, Tooth LR. Diabetes in Pregnancy and Childhood Cognitive Development: A Systematic Review. *Pediatrics.* 2016;137(5).
38. Fraser A, Almqvist C, Larsson H, Langstrom N, Lawlor DA. Maternal diabetes in pregnancy and offspring cognitive ability: sibling study with 723,775 men from 579,857 families. *Diabetologia.* 2014;57(1):102-9.
39. Seshadri S, Oakeshott P, Nelson-Piercy C, Chappell LC. Prepregnancy care. *BMJ.* 2012;344:e3467.
40. Chung CS, Myriantopoulos NC. Factors affecting risks of congenital malformations. II. Effect of maternal diabetes on congenital malformations. *Birth Defects Orig Artic Ser.* 1975;11(10):23-38.

References

41. Karlsson K, Kjellmer I. The outcome of diabetic pregnancies in relation to the mother's blood sugar level. *Am J Obstet Gynecol.* 1972;112(2):213-20.
42. Wahabi HA, Fayed A, Esmaeil S, Elmorshedy H, Titi MA, Amer YS, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. *PLoS One.* 2020;15(8):e0237571.
43. Owens LA, O'Sullivan EP, Kirwan B, Avalos G, Gaffney G, Dunne F, et al. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care.* 2010;33(3):577-9.
44. Egan AM, Danyliv A, Carmody L, Kirwan B, Dunne FP. A Prepregnancy Care Program for Women With Diabetes: Effective and Cost Saving. *J Clin Endocrinol Metab.* 2016;101(4):1807-15.
45. Chatterjee S, Davies MJ, Heller S, Speight J, Snoek FJ, Khunti K. Diabetes structured self-management education programmes: a narrative review and current innovations. *Lancet Diabetes Endocrinol.* 2018;6(2):130-42.
46. Feig DS, Cleave B, Tomlinson G. Long-term effects of a diabetes and pregnancy program: does the education last? *Diabetes Care.* 2006;29(3):526-30.
47. Yee L, Taylor S, Young M, Williams M, Niznik C, Simon M. Evaluation of a Text Messaging Intervention to Support Self-Management of Diabetes During Pregnancy Among Low-Income, Minority Women: Qualitative Study. *JMIR Diabetes.* 2020;5(3):e17794.
48. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. *N Engl J Med.* 2016;375(7):644-54.
49. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet.* 2017;390(10110):2347-59.
50. Pernicova I, Korbonits M. Metformin--mode of action and clinical implications for diabetes and cancer. *Nat Rev Endocrinol.* 2014;10(3):143-56.
51. Feig DS, Donovan LE, Zinman B, Sanchez JJ, Asztalos E, Ryan EA, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2020;8(10):834-44.
52. Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. *Diabet Med.* 2017;34(1):27-36.
53. Feig DS, Murphy K, Asztalos E, Tomlinson G, Sanchez J, Zinman B, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. *BMC Pregnancy Childbirth.* 2016;16(1):173.
54. Xu Q, Xie Q. Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. *Arch Gynecol Obstet.* 2019;299(5):1295-303.
55. Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis. *PLoS Med.* 2019;16(8):e1002848.
56. Jovanovic L, Pettitt DJ. Treatment with insulin and its analogs in pregnancies complicated by diabetes. *Diabetes Care.* 2007;30 Suppl 2:S220-4.
57. Herrera KM, Rosenn BM, Foroutan J, Bimson BE, Al Ibraheemi Z, Moshier EL, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. *Am J Obstet Gynecol.* 2015;213(3):426 e1-7.
58. Hod M, Damm P, Kaaja R, Visser GH, Dunne F, Demidova I, et al. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol.* 2008;198(2):186 e1-7.
59. Hod M, Mathiesen ER, Jovanovic L, McCance DR, Ivanisevic M, Duran-Garcia S, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med.* 2014;27(1):7-13.

References

60. NovoNordisk. A Trial Comparing the Effect and Safety of Insulin Degludec Versus Insulin Detemir, Both in Combination With Insulin Aspart, in the Treatment of Pregnant Women With Type 1 Diabetes. <https://ClinicalTrials.gov/show/NCT03377699>; 2017.
61. Ringholm L. Insulin Fiasp vs. Insulin Novorapid During Pregnancy and Laction in Women With Pre-existing Diabetes. <https://ClinicalTrials.gov/show/NCT03770767>; 2019.
62. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 1998;338(11):701-5.
63. Lin L, Zhu Y, Li B, Yang H, Group AS. Low-dose aspirin in the prevention of pre-eclampsia in China (APPEC study): protocol for a multicentre randomized controlled trial. *Trials.* 2018;19(1):608.
64. Beazley D, Ahokas R, Livingston J, Griggs M, Sibai BM. Vitamin C and E supplementation in women at high risk for preeclampsia: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 2005;192(2):520-1.
65. International Association of Diabetes in Pregnancy Study Group Working Group on Outcome D, Feig DS, Corcoy R, Jensen DM, Kautzky-Willer A, Nolan CJ, et al. Diabetes in pregnancy outcomes: a systematic review and proposed codification of definitions. *Diabetes Metab Res Rev.* 2015;31(7):680-90.
66. Clarke M, Williamson PR. Core outcome sets and systematic reviews. *Syst Rev.* 2016;5:11.
67. WHO. WHO handbook for reporting results of cancer treatment. World Health Organization. 1979.
68. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials.* 2007;8:38.
69. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STANDARDISED Protocol Items: the COS-STAP Statement. *Trials.* 2019;20(1):116.
70. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set-STANDARDS for Reporting: The COS-STAR Statement. *PLoS Med.* 2016;13(10):e1002148.
71. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *BJOG.* 2014;121(10):1181-2.
72. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. *Diabetes Care.* 2014;37(6):1590-6.
73. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract.* 2014;103(2):176-85.
74. Wahabi H, Fayed A, Esmaeil S, Alzeidan R, Elawad M, Tabassum R, et al. Riyadh Mother and Baby Multicenter Cohort Study: The Cohort Profile. *PLoS One.* 2016;11(3):e0150297.
75. Tsur A, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Critical analysis of risk factors for shoulder dystocia. *Arch Gynecol Obstet.* 2012;285(5):1225-9.
76. Shen M, Smith GN, Rodger M, White RR, Walker MC, Wen SW. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. *PLoS One.* 2017;12(4):e0175914.
77. Garne E, Loane M, Dolk H, Barisic I, Addor MC, Arriola L, et al. Spectrum of congenital anomalies in pregnancies with pregestational diabetes. *Birth Defects Res A Clin Mol Teratol.* 2012;94(3):134-40.
78. Kallas-Koeman MM, Kong JM, Klinke JA, Butalia S, Lodha AK, Lim KI, et al. Insulin pump use in pregnancy is associated with lower HbA1c without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. *Diabetologia.* 2014;57(4):681-9.
79. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, et al. Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial. *Diabetes Care.* 2018;41(7):1391-9.
80. Scott EM, Bilous RW, Kautzky-Willer A. Accuracy, User Acceptability, and Safety Evaluation for the FreeStyle Libre Flash Glucose Monitoring System When Used by Pregnant Women with Diabetes. *Diabetes Technol Ther.* 2018;20(3):180-8.

References

81. Carral F, Ayala Mdel C, Fernandez JJ, Gonzalez C, Pinero A, Garcia G, et al. Web-based telemedicine system is useful for monitoring glucose control in pregnant women with diabetes. *Diabetes Technol Ther.* 2015;17(5):349-54.
82. Bartholomew ML, Soules K, Church K, Shaha S, Burlingame J, Graham G, et al. Managing Diabetes in Pregnancy Using Cell Phone/Internet Technology. *Clin Diabetes.* 2015;33(4):169-74.
83. Feig DS, Murphy HR. Continuous glucose monitoring in pregnant women with Type 1 diabetes: benefits for mothers, using pumps or pens, and their babies. *Diabet Med.* 2018;35(4):430-5.
84. Owens LA, Egan AM, Carmody L, Dunne F. Ten Years of Optimizing Outcomes for Women With Type 1 and Type 2 Diabetes in Pregnancy-The Atlantic DIP Experience. *J Clin Endocrinol Metab.* 2016;101(4):1598-605.
85. Egan AM, Galjaard S, Maresh MJA, Loeken MR, Napoli A, Anastasiou E, et al. A core outcome set for studies evaluating the effectiveness of pre-pregnancy care for women with pregestational diabetes. *Diabetologia.* 2017;60(7):1190-6.
86. Egan AM, Bogdanet D, Griffin TP, Kgosidialwa O, Cervar-Zivkovic M, Dempsey E, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. *Diabetologia.* 2020.
87. Egan AM, Smith V, Devane D, Dunne FP. Effectiveness of pre-pregnancy care for women with pregestational diabetes mellitus: protocol for a systematic review of the literature and identification of a core outcomes set using a Delphi survey. *Trials.* 2015;16:356.
88. Bogdanet D, Egan A, Fhelelboom N, Biesty L, Thangaratnam S, Dempsey E, et al. Metabolic follow-up at one year and beyond of women with gestational diabetes treated with insulin and/or oral hypoglycaemic agents: study protocol for the identification of a core outcomes set using a Delphi survey. *Trials.* 2019;20(1):9.
89. Egan AM, Dunne FP, Biesty LM, Bogdanet D, Crowther C, Dempsey E, et al. Gestational diabetes prevention and treatment: a protocol for developing core outcome sets. *BMJ Open.* 2019;9(11):e030574.
90. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs.* 2000;32(4):1008-15.
91. 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;64(4):395-400.
92. Harman NL, Bruce IA, Callery P, Tierney S, Sharif MO, O'Brien K, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials.* 2013;14:70.
93. Jolving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Norgard BM. Prevalence of maternal chronic diseases during pregnancy - a nationwide population based study from 1989 to 2013. *Acta Obstet Gynecol Scand.* 2016;95(11):1295-304.
94. Linden K, Berg M, Adolfsson A, Sparud-Lundin C. Person-centred, web-based support in pregnancy and early motherhood for women with Type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med.* 2018;35(2):232-41.
95. Mostello D. Adherence to a Diabetes Care Regimen Following Text Message Intervention in Pregnant Women With Diabetes. <https://ClinicalTrials.gov/show/NCT03025984>; 2016.
96. Ainuddin JA, Karim N, Zaheer S, Ali SS, Hasan AA. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. *J Diabetes Res.* 2015;2015:325851.
97. Carr KJ, Idama TO, Masson EA, Ellis K, Lindow SW. A randomised controlled trial of insulin lispro given before or after meals in pregnant women with type 1 diabetes--the effect on glycaemic excursion. *J Obstet Gynaecol.* 2004;24(4):382-6.
98. Murphy HR, Kumareswaran K, Elleri D, Allen JM, Caldwell K, Biagioni M, et al. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. *Diabetes Care.* 2011;34(12):2527-9.
99. Meher S, Alfirovic Z. Choice of primary outcomes in randomised trials and systematic reviews evaluating interventions for preterm birth prevention: a systematic review. *BJOG.* 2014;121(10):1188-94; discussion 95-6.

References

100. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *J Perinat Med*. 2014;42(5):543-4.
101. Kgosidialwa O, Bogdanet D, Egan A, O'Shea PM, Biesty L, Devane D, et al. Developing a core outcome set for the treatment of pregnant women with pregestational diabetes-a study protocol. *Trials*. 2020;21(1):1017.
102. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
103. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
104. Bartal M. Detemir Versus NPH for Type 2 Diabetes Mellitus in Pregnancy: A Comparative-effectiveness, Open Label, Randomized Controlled Trial. <https://ClinicalTrials.gov/show/NCT03620890>; 2018.
105. Berry DC, Thomas SD, Dorman KF, Ivins AR, de Los Angeles Abreu M, Young L, et al. Rationale, design, and methods for the Medical Optimization and Management of Pregnancies with Overt Type 2 Diabetes (MOMPOD) study. *BMC Pregnancy Childbirth*. 2018;18(1):488.
106. Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. *PLoS One*. 2015;10(5):e0125712.
107. Brooten D, Youngblut JM, Brown L, Finkler SA, Neff DF, Madigan E. A randomized trial of nurse specialist home care for women with high-risk pregnancies: outcomes and costs. *Am J Manag Care*. 2001;7(8):793-803.
108. Burkart W, Hanker JP, Schneider HP. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. *Gynecol Obstet Invest*. 1988;26(2):104-12.
109. Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER. Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes - observations from a randomized controlled trial. *Diabet Med*. 2013;30(11):1374-81.
110. Demarini S, Mimouni F, Tsang RC, Khoury J, Hertzberg V. Impact of metabolic control of diabetes during pregnancy on neonatal hypocalcemia: a randomized study. *Obstet Gynecol*. 1994;83(6):918-22.
111. di Biase N, Napoli A, Sabbatini A, Borrello E, Buongiorno AM, Fallucca F. Telemedicine in the treatment of diabetic pregnancy. *Ann Ist Super Sanita*. 1997;33(3):347-51.
112. Dieb AS. Effect of Adding Metformin to Insulin Therapy on Pregnancy Outcomes in Women With Uncontrolled Type I Diabetes. In: Mahmoud AKAAGMA, editor.: <https://ClinicalTrials.gov/show/NCT03928340>; 2019.
113. Feghali MN. Metformin for Preeclampsia Prevention in Pregnant Women With Type 1 Diabetes Mellitus. <https://ClinicalTrials.gov/show/NCT03570632>; 2019.
114. Finnegan C, Breathnach F, Dicker P, Fernandez E, Tully E, Higgins M, et al. Investigating the role of early low-dose aspirin in diabetes: A phase III multicentre double-blinded placebo-controlled randomised trial of aspirin therapy initiated in the first trimester of diabetes pregnancy. *Contemp Clin Trials Commun*. 2019;16:100465.
115. Forster DA, Moorhead AM, Jacobs SE, Davis PG, Walker SP, McEgan KM, et al. Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial. *Lancet*. 2017;389(10085):2204-13.
116. Garmy G. Effect of Intrapartum Glucose With Compared to Without Constant Intravenous Insulin on Neonatal Hypoglycemia Among Diabetic Women. A Randomized Controlled Trial. <https://ClinicalTrials.gov/show/NCT03273881>; 2017.
117. Gray L. Utilizing mHealth to Improve Diabetes in an Obstetric Population. <https://ClinicalTrials.gov/show/NCT03504592>; 2018.

References

118. Hanson U, Persson B, Enochsson E, Lennerhagen P, Lindgren F, Lundstrom V, et al. Self-monitoring of blood glucose by diabetic women during the third trimester of pregnancy. *Am J Obstet Gynecol.* 1984;150(7):817-21.
119. Hayden T, Perantie DC, Nix BD, Barnes LD, Mostello DJ, Holcomb WL, et al. Treating prepartum depression to improve infant developmental outcomes: a study of diabetes in pregnancy. *J Clin Psychol Med Settings.* 2012;19(3):285-92.
120. Hickman MA, McBride R, Boggess KA, Strauss R. Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial. *Am J Perinatol.* 2013;30(6):483-90.
121. Horvaticek M, Djelmis J, Ivanisevic M, Oreskovic S, Herman M. Effect of eicosapentaenoic acid and docosahexaenoic acid supplementation on C-peptide preservation in pregnant women with type-1 diabetes: randomized placebo controlled clinical trial. *Eur J Clin Nutr.* 2017;71(8):968-72.
122. Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. *Arch Gynecol Obstet.* 2014;289(5):959-65.
123. Incerpi MH, Fassett MJ, Kjos SL, Tran SH, Wing DA. Vaginally administered misoprostol for outpatient cervical ripening in pregnancies complicated by diabetes mellitus. *Am J Obstet Gynecol.* 2001;185(4):916-9.
124. Jovanovic-Peterson L, Kitzmiller JL, Peterson CM. Randomized trial of human versus animal species insulin in diabetic pregnant women: improved glycemic control, not fewer antibodies to insulin, influences birth weight. *Am J Obstet Gynecol.* 1992;167(5):1325-30.
125. Kjos SL, Henry OA, Montoro M, Buchanan TA, Mestman JH. Insulin-requiring diabetes in pregnancy: a randomized trial of active induction of labor and expectant management. *Am J Obstet Gynecol.* 1993;169(3):611-5.
126. Laatikainen L, Teramo K, Hieta-Heikurainen H, Koivisto V, Pelkonen R. A controlled study of the influence of continuous subcutaneous insulin infusion treatment on diabetic retinopathy during pregnancy. *Acta Med Scand.* 1987;221(4):367-76.
127. Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR. Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. *Am J Obstet Gynecol.* 2003;189(2):507-12.
128. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brondsted L, Jovanovic L, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care.* 2012;35(10):2012-7.
129. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care.* 2007;30(4):771-6.
130. McCance DR, Holmes VA, Maresh MJ, Patterson CC, Walker JD, Pearson DW, et al. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. *Lancet.* 2010;376(9737):259-66.
131. Mimouni F, Miodovnik M, Whitsett JA, Holroyde JC, Siddiqi TA, Tsang RC. Respiratory distress syndrome in infants of diabetic mothers in the 1980s: no direct adverse effect of maternal diabetes with modern management. *Obstet Gynecol.* 1987;69(2):191-5.
132. Min Y, Djahanbakhch O, Hutchinson J, Bhullar AS, Raveendran M, Hallot A, et al. Effect of docosahexaenoic acid-enriched fish oil supplementation in pregnant women with Type 2 diabetes on membrane fatty acids and fetal body composition--double-blinded randomized placebo-controlled trial. *Diabet Med.* 2014;31(11):1331-40.
133. Moninx WM, Zondervan HA, Birnie E, Ris M, Bossuyt PM. High risk pregnancy monitored antenatally at home. *Eur J Obstet Gynecol Reprod Biol.* 1997;75(2):147-53.
134. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ.* 2008;337:a1680.
135. Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *BMJ.* 1999;319(7219):1223-7.

References

136. Ney D, Hollingsworth DR, Cousins L. Decreased insulin requirement and improved control of diabetes in pregnant women given a high-carbohydrate, high-fiber, low-fat diet. *Diabetes Care*. 1982;5(5):529-33.
137. Nor Azlin MI, Nor NA, Sufian SS, Mustafa N, Jamil MA, Kamaruddin NA. Comparative study of two insulin regimes in pregnancy complicated by diabetes mellitus. *Acta Obstet Gynecol Scand*. 2007;86(4):407-8.
138. Notelovitz M. Sulphonylurea therapy in the treatment of the pregnant diabetic. *S Afr Med J*. 1971;45(9):226-9.
139. Perichart-Perera O, Balas-Nakash M, Rodriguez-Cano A, Legorreta-Legorreta J, Parra-Covarrubias A, Vadillo-Ortega F. Low Glycemic Index Carbohydrates versus All Types of Carbohydrates for Treating Diabetes in Pregnancy: A Randomized Clinical Trial to Evaluate the Effect of Glycemic Control. *Int J Endocrinol*. 2012;2012:296017.
140. Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract*. 2002;58(2):115-21.
141. Petrovski G, Dimitrovski C, Bogoev M, Milenkovic T, Ahmeti I, Bitovska I. Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. *Diabetes Technol Ther*. 2011;13(11):1109-13.
142. Polsky S. Pregnancy Intervention With a Closed-Loop System (PICLS) Study. <https://ClinicalTrials.gov/show/NCT03774186>; 2019.
143. Refuerzo JS, Gowen R, Pedroza C, Hutchinson M, Blackwell SC, Ramin S. A pilot randomized, controlled trial of metformin versus insulin in women with type 2 diabetes mellitus during pregnancy. *Am J Perinatol*. 2015;30(2):163-70.
144. Sacks DA, Feig DS, Liu IL, Wolde-Tsadik G. Managing type I diabetes in pregnancy: how near normal is necessary? *J Perinatol*. 2006;26(8):458-62.
145. Rosenberg VA, Eglinton GS, Rauch ER, Skupski DW. Intrapartum maternal glycemic control in women with insulin requiring diabetes: a randomized clinical trial of rotating fluids versus insulin drip. *Am J Obstet Gynecol*. 2006;195(4):1095-9.
146. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. *Diabetes Care*. 2013;36(7):1877-83.
147. Varner MW. Efficacy of home glucose monitoring in diabetic pregnancy. *Am J Med*. 1983;75(4):592-6.
148. Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. *Diabetes Obes Metab*. 2018;20(8):1894-902.
149. Wen SW, White RR, Rybak N, Gaudet LM, Robson S, Hague W, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *BMJ*. 2018;362:k3478.
150. Wojcicki JM, Ladyzynski P, Krzymien J, Jozwicka E, Blachowicz J, Janczewska E, et al. What we can really expect from telemedicine in intensive diabetes treatment: results from 3-year study on type 1 pregnant diabetic women. *Diabetes Technol Ther*. 2001;3(4):581-9.
151. Wright TE, Martin D, Qualls C, Curet LB. Effects of intrapartum administration of invert sugar and D5LR on neonatal blood glucose levels. *J Perinatol*. 2000;20(4):217-8.
152. York R, Brown LP, Samuels P, Finkler SA, Jacobsen B, Persely CA, et al. A randomized trial of early discharge and nurse specialist transitional follow-up care of high-risk childbearing women. *Nurs Res*. 1997;46(5):254-61.
153. Duffy JMN, Ziebland S, von Dadelszen P, McManus RJ. Tackling poorly selected, collected, and reported outcomes in obstetrics and gynecology research. *Am J Obstet Gynecol*. 2019;220(1):71 e1- e4.

References

154. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol.* 2018;96:84-92.
155. Young AE, Brookes ST, Avery KNL, Davies A, Metcalfe C, Blazeby JM. A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. *J Clin Epidemiol.* 2019;115:14-24.
156. Ayman G, Strachan JA, McLennan N, Malouf R, Lowe-Zinola J, Magdi F, et al. The top 10 research priorities in diabetes and pregnancy according to women, support networks and healthcare professionals. *Diabet Med.* 2021:e14588.
157. Fadl HE, Simmons D. Trends in diabetes in pregnancy in Sweden 1998-2012. *BMJ Open Diabetes Res Care.* 2016;4(1):e000221.
158. Albrecht SS, Kuklina EV, Bansil P, Jamieson DJ, Whiteman MK, Kourtis AP, et al. Diabetes trends among delivery hospitalizations in the U.S., 1994-2004. *Diabetes Care.* 2010;33(4):768-73.
159. Eriksen NB, Damm P, Mathiesen ER, Ringholm L. The prevalence of congenital malformations is still higher in pregnant women with pregestational diabetes despite near-normal HbA1c: a literature review. *J Matern Fetal Neonatal Med.* 2019;32(8):1225-9.
160. Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, et al. Diabetes and pregnancy: national trends over a 15 year period. *Diabetologia.* 2018;61(5):1081-8.
161. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER. Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. *Diabetologia.* 2010;53(6):1076-83.
162. Spotti D. Pregnancy in women with diabetic nephropathy. *J Nephrol.* 2019;32(3):379-88.
163. Knight KM, Thornburg LL, Pressman EK. Pregnancy outcomes in type 2 diabetic patients as compared with type 1 diabetic patients and nondiabetic controls. *J Reprod Med.* 2012;57(9-10):397-404.
164. Howorka K, Pumplra J, Gabriel M, Feiks A, Schlusche C, Nowotny C, et al. Normalization of pregnancy outcome in pregestational diabetes through functional insulin treatment and modular outpatient education adapted for pregnancy. *Diabet Med.* 2001;18(12):965-72.
165. Yamamoto JM, Hughes DJF, Evans ML, Karunakaran V, Clark JDA, Morrish NJ, et al. Community-based pre-pregnancy care programme improves pregnancy preparation in women with pregestational diabetes. *Diabetologia.* 2018;61(7):1528-37.
166. Bogdanet D, Reddin C, Macken E, Griffin TP, Fhelelboom N, Biesty L, et al. Follow-up at 1 year and beyond of women with gestational diabetes treated with insulin and/or oral glucose-lowering agents: a core outcome set using a Delphi survey. *Diabetologia.* 2019;62(11):2007-16.
167. Egan AM, Bogdanet D, Biesty L, Kgosidialwa O, McDonagh C, O'Shea C, et al. Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review. *Diabetes Care.* 2020;43(12):3129-35.
168. Young B, Bagley H. Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates. *Res Involv Engagem.* 2016;2:25.
169. Davis K, Gorst SL, Harman N, Smith V, Gargon E, Altman DG, et al. Choosing important health outcomes for comparative effectiveness research: An updated systematic review and involvement of low and middle income countries. *PLoS One.* 2018;13(2):e0190695.
170. Wooldridge G, Murthy S, Kissoon N. Core outcome set in paediatric sepsis in low- and middle-income countries: a study protocol. *BMJ Open.* 2020;10(4):e034960.
171. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S13-S28.
172. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271-81.
173. Metzger BE, Coustan DR, Trimble ER. Hyperglycemia and Adverse Pregnancy Outcomes. *Clin Chem.* 2019;65(7):937-8.
174. Yogev, Chen, Hod, Coustan, Oats, McIntyre, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. *Am J Obstet Gynecol.* 2010;202(3):255 e1-7.

References

175. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Constantino M, Harding AJ, et al. Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment. *Diabetes Care*. 2016;39(1):75-81.
176. Fadl HE, Ostlund IK, Magnuson AF, Hanson US. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. *Diabet Med*. 2010;27(4):436-41.
177. O'Sullivan EP, Avalos G, O'Reilly M, Dennedy MC, Gaffney G, Dunne F, et al. Atlantic Diabetes in Pregnancy (DIP): the prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. *Diabetologia*. 2011;54(7):1670-5.
178. Guerrero-Romero F, Aradillas-Garcia C, Simental-Mendia LE, Monreal-Escalante E, de la Cruz Mendoza E, Rodriguez-Moran M. Birth weight, family history of diabetes, and metabolic syndrome in children and adolescents. *J Pediatr*. 2010;156(5):719-23, 23 e1.
179. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008;300(24):2886-97.
180. Scholtens DM, Kuang A, Lowe LP, Hamilton J, Lawrence JM, Leberthal Y, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism. *Diabetes Care*. 2019;42(3):381-92.
181. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373(9677):1773-9.
182. Bennett WL, Robinson KA, Saldanha IJ, Wilson LM, Nicholson WK. High priority research needs for gestational diabetes mellitus. *J Womens Health (Larchmt)*. 2012;21(9):925-32.
183. Di Biase N, Balducci S, Lencioni C, Bertolotto A, Tumminia A, Dodesini AR, et al. Review of general suggestions on physical activity to prevent and treat gestational and pre-existing diabetes during pregnancy and in postpartum. *Nutr Metab Cardiovasc Dis*. 2019;29(2):115-26.
184. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. *Cochrane Database Syst Rev*. 2017;1:CD011967.
185. Healy P, Gordijn SJ, Ganzevoort W, Beune IM, Baschat A, Khalil A, et al. A Core Outcome Set for the prevention and treatment of fetal GROWth restriction: deVeloPping Endpoints: the COSGROVE study. *Am J Obstet Gynecol*. 2019;221(4):339 e1- e10.
186. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132.
187. Khan KS, Romero R, Chief Editors of Journals participating in CI. The CROWN initiative: journal editors invite researchers to develop core outcomes in women's health. *Am J Obstet Gynecol*. 2014;211(6):575-6.
188. 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;14(11):e1002447.
189. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. *Trials*. 2017;18(Suppl 3):280.
190. Bain E, Middleton P, Crowther CA. Progressing towards standard outcomes in gestational diabetes Cochrane reviews and randomised trials. *Aust N Z J Obstet Gynaecol*. 2016;56(1):113-6.
191. Excellence. NifHaC. Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period. National Institute for Health and Care Excellence: Clinical Guidelines. London 2015.
192. Wahabi HA, Alzeidan RA, Esmaeil SA. Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis. *BMC Public Health*. 2012;12:792.
193. Dwan K, Gamble C, Williamson PR, Kirkham JJ, Reporting Bias G. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. *PLoS One*. 2013;8(7):e66844.
194. Hui AL, Sevenhuysen G, Harvey D, Salamon E. Stress and anxiety in women with gestational diabetes during dietary management. *Diabetes Educ*. 2014;40(5):668-77.
195. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47(1):207-14.

References

196. OMERACT. Outcome Measures in Rheumatology. Accessed 5 March 2020. Available from <https://www.omeract.org/>.
197. Egan AM, Bogdanet D, Griffin TP, Kgosidialwa O, Cervar-Zivkovic M, Dempsey E, et al. A core outcome set for studies of gestational diabetes mellitus prevention and treatment. *Diabetologia*. 2020;63(6):1120-7.
198. Nielsen KK, O'Reilly S, Wu N, Dasgupta K, Maindal HT. Development of a core outcome set for diabetes after pregnancy prevention interventions (COS-DAP): a study protocol. *Trials*. 2018;19(1):708.
199. COMET. W. Accessed 5 March 2020. Available from <https://comet-initiative.org>.
200. What is public involvement in research? Accessed 5 March 2020. Available from <https://www.invo.org.uk/find-out-more/what-is-publicinvolvement-in-research-2/>
201. Smith H, Horobin A, Fackrell K, Colley V, Thacker B, Hall DA, et al. Defining and evaluating novel procedures for involving patients in Core Outcome Set research: creating a meaningful long list of candidate outcome domains. *Res Involv Engagem*. 2018;4:8.
202. Biggane AM, Williamson PR, Ravaud P, Young B. Participating in core outcome set development via Delphi surveys: qualitative interviews provide pointers to inform guidance. *BMJ Open*. 2019;9(11):e032338.
203. Keeley T, Williamson P, Callery P, Jones LL, Mathers J, Jones J, et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. *Trials*. 2016;17(1):230.
204. Gargon E, Williamson PR, Young B. Improving core outcome set development: qualitative interviews with developers provided pointers to inform guidance. *J Clin Epidemiol*. 2017;86:140-52.
205. Duffy J, Thompson T, Hinton L, Salinas M, McManus RJ, Ziebland S, et al. What outcomes should researchers select, collect and report in pre-eclampsia research? A qualitative study exploring the views of women with lived experience of pre-eclampsia. *BJOG*. 2019;126(5):637-46.
206. James Lind Alliance. Diabetes and Pregnancy Priority Sharing Partnerships. Accessed 5 March 2020. Available from <https://www.jla.nihr.ac.uk/priority-setting-partnerships/diabetes-andpregnancy/>
207. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *Int J Gynaecol Obstet*. 2015;131 Suppl 3:S173-211.
208. The Millennium Project. Accessed 5 March 2020. Available from <http://www.millenniumproject.org/rtd-general/>.
209. Schoenen J. Guidelines for trials of drug treatments in tension-type headache. First edition: International Headache Society Committee on Clinical Trials. *Cephalalgia*. 1995;15(3):165-79.
210. Bendtsen L, Bigal ME, Cerbo R, Diener HC, Holroyd K, Lampl C, et al. Guidelines for controlled trials of drugs in tension-type headache: second edition. *Cephalalgia*. 2010;30(1):1-16.
211. Kirkham JJ, Bracken M, Hind L, Pennington K, Clarke M, Williamson PR. Industry funding was associated with increased use of core outcome sets. *J Clin Epidemiol*. 2019;115:90-7.
212. Akinremi A, Turnbull AE, Chessare CM, Bingham CO, 3rd, Needham DM, Dinglas VD. Delphi panelists for a core outcome set project suggested both new and existing dissemination strategies that were feasibly implemented by a research infrastructure project. *J Clin Epidemiol*. 2019;114:104-7.
213. Green Park Collaborative. A multi-pronged strategy to improve the relevance, usefulness, and comparability of outcomes in clinical research, 2018. Center for Medical Technology Policy. Accessed 14 August 2020. Available from www.cmtpn.net/docs/resources/COS_Strategy_Paper_Final.pdf.
214. National Institutes of Health, National Laboratory of Medicine. Common Data Element (CDE) Resource Portal. Accessed 5 March 2020. Available from <https://www.nlm.nih.gov/cde/glossary.html>.

References

215. Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ*. 2017;357:j2262.

Appendix 1

Appendix 1 Full Search Strategy for Paper 3 and 4 (A core outcome set for the treatment of pregnant women with pregestational diabetes: an international consensus study)

EMBASE (via EBSCOHOST platform). Search up to 16 January 2020.		
No.	Query	Results
#11	((('pre-gestational diabetes':ti,ab,kw OR 'pregestational diabetes':ti,ab,kw) OR (('preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw) OR (('type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw)) AND (intervention:ti,ab,kw OR therapy:ti,ab,kw OR treatment:ti,ab,kw OR education:ti,ab,kw)) AND 'human'/de AND ('randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)	283
#10	((('pre-gestational diabetes':ti,ab,kw OR 'pregestational diabetes':ti,ab,kw) OR (('preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw) OR (('type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw)) AND (intervention:ti,ab,kw OR therapy:ti,ab,kw OR treatment:ti,ab,kw OR education:ti,ab,kw)) AND 'human'/de	2645
#9	((('pre-gestational diabetes':ti,ab,kw OR 'pregestational diabetes':ti,ab,kw) OR (('preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw) OR (('type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw)) AND (intervention:ti,ab,kw OR therapy:ti,ab,kw OR treatment:ti,ab,kw OR education:ti,ab,kw))	2879
#8	intervention:ti,ab,kw OR therapy:ti,ab,kw OR treatment:ti,ab,kw OR education:ti,ab,kw	8135469
#7	('pre-gestational diabetes':ti,ab,kw OR 'pregestational diabetes':ti,ab,kw) OR (('preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw) OR (('type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw)	8936
#6	('type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw	7276
#5	('preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw) AND pregnan*:ti,ab,kw	680
#4	pregnan*:ti,ab,kw	660805
#3	'type 1 diabetes':ti,ab,kw OR t1dm:ti,ab,kw OR 'insulin dependent diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR t2dm:ti,ab,kw OR 'insulin independent diabetes':ti,ab,kw	268667
#2	'preexisting diabetes':ti,ab,kw OR 'pre-existing diabetes':ti,ab,kw	1670
#1	'pre-gestational diabetes':ti,ab,kw OR 'pregestational diabetes':ti,ab,kw	1452
COCHRANE Library. Searched up to 19 January 2020.		
ID	Search	Hits
#1	MeSH descriptor: [Pregnancy in Diabetics] explode all trees	303
#2	("type 1 diabetes" OR T1DM OR "insulin dependent diabetes" OR "type 2 diabetes" OR T2DM OR "insulin independent diabetes" OR "pregestational diabetes" OR "pre-gestational diabetes" OR "preexisting diabetes" OR "pre-existing diabetes"):ti,ab,kw (Word variations have been searched)	42407
#3	#1 AND #2	98

Appendix 1

#4	(pregnan*):ti,ab,kw (Word variations have been searched)	60455	
#5	("type 1 diabetes" OR T1DM OR "insulin dependent diabetes" OR "type 2 diabetes" OR T2DM OR "insulin independent diabetes" OR "preexisting diabetes" OR "pre-existing diabetes"):ti,ab,kw (Word variations have been searched)	42346	
#6	#4 AND #5	1300	
#7	(Intervention OR treatment OR therapy OR management OR education):ti,ab,kw (Word variations have been searched)	1117350	
#8	#6 AND #7	1158	
#9	#3 AND #7	85	
#10	#8 OR #9	1164	
#11	("randomized controlled trial"):ti,ab,kw (Word variations have been searched)	474488	
#12	#10 AND #11	372 Trials (333) Reviews (39)	
CINAHL (via EBSCO host platform). Searched up to 19 January 2020.			
#	Query	Limiters/Expanders	Results
S11	S9 OR S10	Limiters - Randomized Controlled Trials; Language: English; Sex: Female Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	31
S10	S7 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	765
S9	S5 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	616
S8	AB intervention OR treatment OR therapy OR program OR programme OR strategy OR management OR education	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,444,628
S7	S3 AND S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,691
S6	AB Pregnan*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	89,473
S5	S1 AND S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,010
S4	S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	109,529
S3	AB "Type 1 diabetes" OR T1DM OR "Insulin dependent diabetes" OR "Type 2 diabetes" OR T2DM OR "Insulin independent diabetes"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	109,330
S2	AB "pregestational diabetes" OR "pre-gestational diabetes"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	280
S1	(MH "Pregnancy in Diabetes+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	7,976
MEDLINE (Via Ovid platform) Searched up to 19 January 2020.			
#	Searches		Results

Appendix 1

1	exp Pregnancy in Diabetics/	12695
2	limit 1 to (female and humans and english and (clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial) and "therapy (maximizes sensitivity)" and pregnancy - wide)	326
3	exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/	188981
4	limit 3 to (female and humans and english and (clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial) and "therapy (maximizes sensitivity)" and pregnancy - wide)	303
5	pregestational diabetes OR pre-gestational diabetes {Including Related Terms}	10955
6	limit 5 to (female and humans and english and (clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial) and "therapy (maximizes sensitivity)" and pregnancy - wide)	261
7	preexisting diabetes OR pre-existing diabetes {Including Related Terms}	11446
8	limit 7 to (female and humans and english and (clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial) and "therapy (maximizes sensitivity)" and pregnancy - wide)	234
9	2 or 4 or 6 or 8	668
10	9 not "gestational diabetes".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	327
Web of Science. Searched up to 27 January 2020.		
Title searches in title, abstract, author keywords, and Keywords Plus		
#	Searches	Result
11	(#10) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	480
10	#9 AND #8 AND #7 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	499
9	TOPIC: (randomized controlled trial OR randomised controlled trial OR clinical trial OR RCT) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	886,343
8	TOPIC: (intervention OR management OR treatment OR therapy OR education) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	9,153,242
7	#6 OR #5 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	8,192
6	#4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	6,957
5	#4 AND #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	741
4	TOPIC: (pregnan* OR pregnant wom?n) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	502,146

Appendix 1

3	TOPIC: (type 1 diabetes OR T1DM OR insulin dependent diabetes OR type 2 diabetes OR T2DM OR insulin independent diabetes) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	264,290
2	TOPIC: (preexisting diabetes OR pre-existing diabetes) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	3,609
1	TOPIC: (pregestational diabetes OR pre-gestational diabetes) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	1,181

Appendix 2

Appendix 2 List of All Included Studies for Paper 4 (A core outcome set for studies of gestational diabetes mellitus prevention and treatment)

KEY	TITLE	Year	JOURNAL	ISSN	VOLUME	ISSUE	PAGES	AUTHORS
GDM Prevention Trials								
10980530. Language: English. Entry Date: 20110107. Revision Date: 20151022. Publication Type: journal article	Diet and exercise interventions for preventing gestational diabetes mellitus	2015	Cochrane Database of Systematic Reviews		4	N/A		Bain, E. and Crane, M. and Tieu, J. and Han, S. and Crowther, C. A. and Middleton, P. and Bain, Emily and Crane, Morven and Tieu, Joanna and Han, Shanshan and Crowther, Caroline A. and Middleton, Philippa
CN-01108757	Myo-inositol Supplementation for Prevention of Gestational Diabetes in Obese Pregnant Women: a Randomized Controlled Trial	2015	Obstetrics and gynecology	1873-233X	126	2	3104-3115	D'Anna, R. and Di Benedetto, A. and Scilipoti, A. and Santamaria, A. and Interdonato, M. L. and Petrella, E. and Neri, I. and Pintaudi, B. and Corrado, F. and Facchinetti, F.
CN-01070801	The effect of a personalized intervention on weight gain and physical activity among pregnant women in China	2015	International journal of gynaecology and obstetrics		12	2	1384-1391	Jing, W. and Huang, Y. and Liu, X. and Luo, B. and Yang, Y. and Liao, S.
103119970. Language: English. Entry Date: 20151113. Revision Date: 20160531. Publication Type: Article	Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials	2015	Obstetric Medicine	1753-495X (1753-495X)	8	2	68-85	Madhuvrata, P. and Govinden, Gemma and Bustani, R. and Song, S. and Farrell, T. A.
109777609. Language: English. Entry Date: 20150612. Revision Date: 20151025. Publication Type: journal article	Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis	2015	Obstetrics & Gynecology		15	3	57-62	Russo, Lindsey M. and Nobles, Carrie and Ertel, Karen A. and Chasan-Taber, Lisa and Whitcomb, Brian W.
CN-01255648	Supplementation of vitamin D in pregnancy and its correlation with foeto-maternal outcome	2015	Clinical endocrinology	1365-2265	83	4	5364-541	Sablok, A. and Batra, A. and Thariani, K. and Batra, A. and Bharti, R. and Aggarwal, A. R. and Kabi, B. C. and Chellani, H.
CN-01105979	Lifestyle intervention for gestational diabetes mellitus prevention: a cluster-randomized controlled study	2015	Chronic diseases and translational medicine	2095-882X	1	3	1694-174	Wang, S. and Ma, J. M. and Yang, H. X.
26256041	Fish Oil Supplementation does not Reduce Risks of Gestational Diabetes Mellitus, Pregnancy-Induced Hypertension, or Pre-Eclampsia: A Meta-Analysis of Randomized Controlled Trials	2015	Medical Science Monitor		21		2322-30	Chen, B. and Ji, X. and Zhang, L. and Hou, Z. and Li, C. and Tong, Y.
WOS:000356493300002	Exercise Is Associated with a Reduction in Gestational Diabetes Mellitus	2015	Medicine and Science in Sports and Exercise	0195-9131	47	7	1328-1333	Cordero, Y. and Mottola, M. F. and Vargas, J. and Blanco, M. and Barakat, R.
WOS:000361653200018	Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial	2015	Lancet Diabetes & Endocrinology	2213-8587	3	10	77-87	Poston, L. and Bell, R. and Croker, H. and Flynn, A. C. and Godfrey, K. M. and Goff, L. and Hayes, L. and Khazaezadeh, N. and Nelson, S. M. and Oteng-Ntim, E. and Pasupathy, D. and Patel, N. and Robson, S. C. and Sallis, J. and Sengco, T. A. B. and Sattar, N. and Seed, P. T. and Wardle, J. and Whitworth, M. K. and Briley, A. L. and Consortium, Upbeat Trial
WOS:000350213200004	Nutritional Manipulation for the Primary Prevention of Gestational Diabetes Mellitus: A Meta-Analysis of Randomised Studies	2015	Plos One	1932-6203	10	2		Rogozinska, E. and Chamillard, M. and Hitman, G. A. and Khan, K. S. and Thangaratnam, S.
WOS:000380131300036	Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial	2015	Journal of Maternal-Fetal & Neonatal Medicine	1476-7058	26	9	3234-3237	Santamaria, A. and Di Benedetto, A. and Petrella, E. and Pintaudi, B. and Corrado, F. and D'Anna, R. and Neri, I. and Facchinetti, F.
115240207. Language: English. Entry Date: 20160728. Revision Date: 20160728. Publication Type: Article	The effectiveness of lifestyle intervention in early pregnancy to prevent gestational diabetes mellitus in Chinese overweight and obese women: A quasi-experimental study	2016	Applied Nursing Research		30		125-130	Yu, Sun and Hong, Zhao
CN-01141189	Gestational Diabetes Mellitus Can Be Prevented by Lifestyle Intervention: the Finnish Gestational Diabetes Prevention Study (RADIEL): a Randomized Controlled Trial	2016	Diabetes care	0149-5992	39	1	248-253	Koivusalu, S. B. and Räsänen, K. and Klemetti, M. M. and Roine, R. P. and Lindström, J. and Erkkola, M. and Kaaja, R. J. and Pääkkönen-Alho, M. and Tiitinen, A. and Huvinen, E. and al., et
CN-01379178	Dietary patterns in obese pregnant women; influence of a behavioral intervention of diet and physical activity in the UPBEAT randomized controlled trial	2016	International journal of behavioral nutrition and physical activity		13	1	124-134	Flynn, A. C. and Seed, P. T. and Patel, N. and Barr, S. and Bell, R. and Briley, A. L. and Godfrey, K. M. and Nelson, S. M. and Oteng-Ntim, E. and Robinson, S. M. and al., et
CN-01208169	Regular Exercise to Prevent the Recurrence of Gestational Diabetes Mellitus: a Randomized Controlled Trial	2016	Obstetrics and gynecology	1873-233X	12	4	819-826	Guelfi, K. J. and Ong, M. J. and Crisp, N. A. and Fournier, P. A. and Wallman, K. E. and Grove, J. R. and Doherty, D. A. and Newnham, J. P.

Appendix 2

									82
									7
CN-01379780	A Daily Snack Containing Leafy Green Vegetables, Fruit, and Milk before and during Pregnancy Prevents Gestational Diabetes in a Randomized, Controlled Trial in Mumbai, India	2 0 1 6	Journal of nutrition	1 4 6	7 14 53 54 60 5			Sahariah, S. A. and Potdar, R. D. and , G and hi, M. and Kehoe, S. H. and Brown, N. and Sane, H. and Coakley, P. J. and Marley-Zagar, E. and Chopra, H. and Shivshankaran, D. and al., et	
114972605. Language: English. Entry Date: 20170923. Revision Date: 20181206. Publication Type: Article	The effect of vitamin D supplementation on gestational diabetes in high-risk women: Results from a randomized placebo-controlled trial	2 0 1 6	Journal of Research in Medical Sciences	2 1	1 -	01		Shahgheibi, Shole and Farhadifar, Fariba and Pouya, Bahar	
WOS:000383354300009	Exercise Training and Weight Gain in Obese Pregnant Women: A Randomized Controlled Trial (ETIP Trial)	2 0 1 6	Plos Medicine	1549-1277	1 3	7		Garns, K. K. and Morkved, S. and Salvesen, O. and Moholdt, T.	
WOS:000367331800020	Randomized Controlled Trial Investigating the Effects of a Low-Glycemic Index Diet on Pregnancy Outcomes in Women at High Risk of Gestational Diabetes Mellitus: The GI Baby 3 Study	2 0 1 6	Diabetes Care		3 9	1 -	31	Markovic, T. P. and Muirhead, R. and Overs, S. and Ross, G. P. and Louie, J. C. Y. and Kizirian, N. and Denyer, G. and Petocz, P. and Hyett, J. and , Br and -Miller, J. C.	
WOS:000374705100019	Self-weighting and simple dietary advice for overweight and obese pregnant women to reduce obstetric complications without impact on quality of life: a randomised controlled trial	2 0 1 6	Bjog-an International Journal of Obstetrics and Gynaecology	1470-0328	1 2 3	6 5- 97 3	96	McCarthy, E. A. and Walker, S. P. and Ugoni, A. and Lappas, M. and Leong, O. and Shub, A.	
27417680	Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials	2 0 1 6	Obesity Reviews		1 7	1 0	96	Song, C. and Li, J. and Leng, J. and Ma, R. C. and Yang, X.	
121157731. Language: English. Entry Date: 20170604. Revision Date: 20180121. Publication Type: journal article	A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women	2 0 1 7	American Journal of Obstetrics & Gynecology		2 1 6	2	N. PA G- N. PA G	Wang, Chen and Wei, Yumei and Zhang, Xiaoming and Zhang, Yue and Xu, Qianqian and Sun, Yiyi and Su, Shiping and Zhang, Li and Liu, Chunhong and Feng, Yaru and Shou, Chong and Guelfi, Kym J. and Newnham, John P. and Yang, Huixia	
120750506. Language: English. Entry Date: 20180720. Revision Date: 20180723. Publication Type: journal article	Primary prevention of gestational diabetes mellitus through nutritional factors: a systematic review	2 0 1 7	BMC Pregnancy & Childbirth	1471-2393	1 7		01	Donazar-Ezcurra, Mikel and Lpez-del Burgo, Cristina and Bes-Rastrollo, Maira	
CN-01614769	A randomized controlled trial of exercise during pregnancy on maternal and neonatal outcomes: results from the PAMELA study	2 0 1 7	International journal of behavioral nutrition and physical activity		1 4	1 5	17	da Silva, S. G. and Hallal, P. C. and Domingues, M. R. and Bertoldi, A. D. and Silveira, M. F. D. and Bassani, D. and da Silva, I. C. M. and da Silva, B. G. C. and Coll, C. V. N. and Evenson, K.	
CN-01622817	The prevention of gestational diabetes mellitus with antenatal oral inositol supplementation: a randomized controlled trial. Diabetes care 2017;40: 759-763	2 0 1 7	Diabetes care	0149-5992	4 0	1 2	e1 72		
CN-01600866	Adherence to a lifestyle programme in overweight/obese pregnant women and effect on gestational diabetes mellitus: a randomized controlled trial	2 0 1 7	Maternal & child nutrition	1740-8709	1 3	3		Bruno, R. and Petrella, E. and Bertarini, V. and Pedrielli, G. and Neri, I. and Facchinetti, F.	
124820999. Language: English. Entry Date: 20180117. Revision Date: 20190131. Publication Type: Article	A systematic review of interventions for Hispanic women with or at risk of Gestational diabetes mellitus (GDM)	2 0 1 7	Sexual & Reproductive HealthCare		1 3		14	Carolan-Olah, Mary and Duarte-Gardea, Maria and Lechuga, Julia	
126012269. Language: English. Entry Date: 20171113. Revision Date: 20180722. Publication Type: journal article	A Medically Supervised Pregnancy Exercise Intervention in Obese Women: A Randomized Controlled Trial	2 0 1 7	Obstetrics & Gynecology		1 3 0	5	10 01 -	Daly, Niamh and Farren, Maria and McKeating, Aoife and O'Kelly, Ruth and Stapleton, Mary and Turner, Michael J. and O'Kelly, Ruth	
CN-01332075	A randomized lifestyle intervention preventing gestational diabetes: effects on self-rated health from pregnancy to postpartum	2 0 1 7	Journal of psychosomatic obstetrics and gynaecology	1743-8942			1 6	Engberg, E. and Stach-Lempinen, B. and Rono, K. and Kautiainen, H. and Eriksson, J. G. and Koivusalo, S. B.	
CN-01299354	Lifestyle intervention to limit gestational weight gain: the Norwegian Fit for Delivery randomised controlled trial	2 0 1 7	BJOG		1 2 4	1	97	Sagedal, L. R. and rverby, N. C. and Bere, E. and Torstveit, M. K. and Lohne-Seiler, H. and Smstuen, M. and Hillesund, E. R. and Henriksen, T. and Vistad, I.	
CN-01366875	Effect of physical activity and/or healthy eating on gdm risk: the dali lifestyle study	2 0 1 7	Journal of clinical endocrinology and metabolism	0021-972X	1 0 2	3	90 3 60 91 3	Simmons, D. and Devlieger, R. and Van Assche, A. and Jans, G. and Galjaard, S. and Corcoy, R. and Adelantado, J. M. and Dunne, F. and Desoye, G. and Harreiter, J. and al., et	
122767426. Language: English. Entry Date: 20170505. Revision Date: 20170505. Publication Type: Article	Early pregnancy probiotic supplementation with Lactobacillus rhamnosus HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial	2 0 1 7	British Journal of Nutrition		1 1 7	6	80 4- 81 3	Wickens, Kristin L. and Barthow, Christine A. and Murphy, Rinki and Abels, Peter R. and Maude, Robyn M. and Stone, Peter R. and Mitchell, Edwin A. and Stanley, Thorsten V. and Purdie, Gordon L. and Kang, Janice M. and Hood, Fiona E. and Rowden, Judy L. and Barnes, Phillipa K. and Fitzharris, Penny F. and Crane, Julian	
29049303	A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM prevention study	2 1 1 7	PLoS ONE [Electronic Resource]		1 2	1 0	e0 18 58 73	Assaf-Balut, C. and Garcia de la Torre, N. and Duran, A. and Fuentes, M. and Bordiu, E. and Del Valle, L. and Familiar, C. and Ortola, A. and Jimenez, I. and Herraiz, M. A. and Izquierdo, N. and Perez, N. and Torrejon, M. J. and Ortega, M. I. and Illana, F. J. and Runkle, I. and de Miguel, M. P. and Montanez, C. and Barabash, A. and Cuesta, M. and Rubio, M. A. and Calle-Pascual, A. L.	

Appendix 2

RN1748	Metformin in women at high risk of gestational diabetes mellitus	2 0 1 8	Diabetes & metabolism	1878-1780; 1262-3636	4 4 3 30	3 0 30 2	Brink, H. S. and Alkemade, M. and van der Lely, A. J. and van der Linden, J.
CN-01464677	Cost-effectiveness of healthy eating and/or physical activity promotion in pregnant women at increased risk of gestational diabetes mellitus: economic evaluation alongside the DALI study, a European multicenter randomized controlled trial	2 0 1 8	International journal of behavioral nutrition and physical activity		1 5	1	Broekhuizen, K. and Simmons, D. and Devlieger, R. and van Assche, A. and Jans, G. and Galjaard, S. and Corcoy, R. and Adelantado, J. M. and Dunne, F. and Desoye, G. and al., et
CN-01668548	Evaluating the effects of mobile health intervention on weight management, glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus	2 0 1 8	Journal of Endocrinologica Investigation	1720-8386			Guo, H. and Zhang, Y. and Li, P. and Zhou, P. and Chen, L. M. and Li, S. Y.
CN-01650263	Magnesium-zinc-calcium-vitamin D co-supplementation improves glycemic control and markers of cardiometabolic risk in gestational diabetes: a randomized, double-blind, placebo-controlled trial	2 0 1 8	Physiologie appliquee, nutrition et [Applied physiology, nutrition, and metabolism]	1715-5320 (Electron)	4 3	6 56 58 57 0	Karamali, M. and Bahramimoghadam, S. and Sharifzadeh, F. and Asemi, Z.
WOS:00044292090001	Prevention of gestational diabetes with a prepregnancy lifestyle intervention - findings from a randomized controlled trial	2 0 1 8	International Journal of Womens Health	1179-1411	1 0	49 3-50 1	Rono, K. and Stach-Lempinen, B. and Eriksson, J. G. and Poyhonen-Alho, M. and Klemetti, M. M. and Roine, R. P. and Huvinen, E. and Andersson, S. and Laivuori, H. and Valkama, A. and Meinila, J. and Kautiainen, H. and Tiitinen, A. and Koivusalo, S. B.
WOS:000443000400020	Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: a secondary analysis from 3 RCTs	2 0 1 8	American Journal of Obstetrics and Gynecology		2 1 9	3 6	Santamaria, A. and Alibr and i, A. and Di Benedetto, A. and Pintaudi, B. and Corrado, F. and Facchinetti, F. and D'Anna, R.
WOS:000443733500005	Effect of a lifestyle intervention during pregnancy-findings from the Finnish gestational diabetes prevention trial (RADIEL)	2 0 1 8	Journal of Perinatology		3 8	9 11 57 - 11 64	Rono, K. and Grotenfelt, N. E. and Klemetti, M. M. and Stach-Lempinen, B. and Huvinen, E. and Meinila, J. and Valkama, A. and Tiitinen, A. and Roine, R. P. and Poyhonen-Alho, M. and Andersson, S. and Laivuori, H. and Kautiainen, H. and Eriksson, J. G. and Koivusalo, S. B.
WOS:000442236900020	Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial	2 0 1 8	Journal of Clinical Endocrinology & Metabolism		1 0 3	8 36 - 29 48	Rostami, M. and Tehrani, F. R. and Simbar, M. and , Yar and i, R. B. and Minooee, S. and Hollis, B. W. and Hosseinpanah, F.
WOS:000432224600003	Effectiveness of Metformin in the Prevention of Gestational Diabetes Mellitus in Obese Pregnant Women	2 0 1 8	Revista Brasileira De Ginecologia E Obstetricia		4 0	4 18 0 18 7	Sales, W. B. and do Nascimento, I. B. and Dienstmann, G. and de Souza, M. L. R. and da Silva, G. D. and Silva, J. C.
WOS:000425733500012	Effects of low-glycemic-index diets in pregnancy on maternal and newborn outcomes in pregnant women: a meta-analysis of randomized controlled trials	2 0 1 8	European Journal of Nutrition	1436-6207	5 7	1 16 7- 17 7	Zhang, R. and Han, S. F. and Chen, G. C. and Li, Z. N. and Silva-Zolezzi, I. and Pares, G. V. and Wang, Y. and Qin, L. Q.
	Effects of a lifestyle intervention during pregnancy to prevent excessive gestational weight gain in routine care - the cluster-randomised Gelis trial	2 1 9	Bmc Medicine	1741-7015	1 7		Kunath, J. and Gunther, J. and Rauh, K. and Hoffmann, J. and Stecher, L. and Rosenfeld, E. and Kick, L. and Ulm, K. and Hauner, H.
GDM Treatment Trials							
113836445	Effect of Aerobic Dance Exercise on Blood Pressure of Normotensive Pregnant Women Diagnosed with Gestational Diabetes at Federal Medical Centre, Owerri, South East Nigeria	2 0 1 5	Indian Journal of Physiotherapy & Occupational Therapy	0973-5666	9 4	12 4- 12 8	Daniel, Jovita A. and Venkateswarlu, K. and Ezeugwu, Clifford C.
rayyan-3785124	Metformin versus insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle Bu Teaching Hospital: A randomized clinical trial	2 0 1 5	PLoS ONE		1 0	5 12 57 12	Beyuo, T. and Obed, S. A. and Adjepong-Yamoah, K. K. and Bugyei, K. A. and Oppong, S. A. and Marfoh, K.
CN-01052278	Comparison of glyburide and insulin in women with gestational diabetes mellitus and associated perinatal outcome: a randomized clinical trial	2 0 1 5	Acta medica iranica		5 3	2 97 81 03	Mirzamoradi, M. and Heidar, Z. and Faalpoor, Z. and Naeiji, Z. and Jamali, R.
CN-01098590	Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes Presented in poster format at the 35th annual meeting of the Society for Maternal-Fetal Medicine, San Diego, CA, Feb. 2-7, 2015	2 0 1 5	American journal of clinical obstetrics and gynecology	0002-9378 Y2 - 2010 /03//	2 3	3 42 6e 1a 1a 42 6e 7	Herrera, K. M. and Rosenn, B. M. and Foroutan, J. and Bimson, B. E. and Al Ibraheemi, Z. and Moshier, E. L. and Brustman, L. E.
CN-01048447	Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country: a randomized control trial	2 0 1 5	Diabetes research and clinical practice	0168-8227	1 0 7	2 29 0a 29 9	Ainuddin, J. and Karim, N. and Hasan, A. A. and Naqvi, S. A.
CN-01085159	Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial	2 0 1 5	American journal of clinical nutrition		1 0 2	1 22 2a 22 9	Asemi, Z. and Karamali, M. and Jamilian, M. and Foroozanfar, F. and Bahmani, F. and Heidarzadeh, Z. and Benisi-Kohansal, S. and Surkan, P. J. and Esmailzadeh, A.
CN-01103272	Web-Based Telemedicine System is Useful for Monitoring Glucose Control in Pregnant Women with Diabetes	2 0 1 5	Diabetes technology & therapeutics	1557-8593	1 7	5 34 9a 29 35 4	Carral, F. and Ayala, M. D. C. and , Fern and ez, J. J. and Gonzalez, C. and Pinerio, A. and Garcia, G. and Canavate, C. and Jimenez, A. I. and Garcia, C.
111282518	Is there a value for probiotic supplements in gestational diabetes mellitus? A randomized clinical trial	2 0 1 5	Journal of Health, Population & Nutrition		3 3	01 - Au g	Dolatkhah, Neda and Hajifaraji, Majid and Abbasizadeh, Fatemeh and Aghamohammadzadeh, Naser and Mehrabi, Yadollah and Abbasi, Mehran Mesgari and Mesgari Abbasi, Mehran

Appendix 2

110260176. Language: English. Entry Date: 20160113. Revision Date: 20180629. Publication Type: journal article	Randomized controlled study in pregnancy on treatment of marked hyperglycemia that is short of overt diabetes	2 0 1 5	Acta Obstetrica et Gynecologica Scandinavica	9 4	1 1	11 81 - 11 87	Fadl, Helena E. and GÅrdefors, Susanne and Hjertberg, Ragnhild and Nord, Eva and Persson, Bengt and Schwarcz, Erik and Å...man, Jan and Å–stlund, Ingrid K. and Hanson, Ulf S. B.
CN-01052445	Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide—a randomised controlled trial	2 0 1 5	Australian & New Zealand journal of obstetrics & gynaecology	5 5	1 -	47 æ 05 2	George, A. and Mathews, J. E. and Sam, D. and Beck, M. and Benjamin, S. J. and Abraham, A. and Antonisamy, B. and Jana, A. K. and Thomas, N.
CN-01161668	Application of seamless care service with multidisciplinary diagnosis and treatment in patients with gestational diabetes	2 0 1 5	International journal of clinical and experimental medicine	1940-5901	8 9	16 68 8å 00 16 69 3	Jie, S. Q. and Liang, X. and Hong, P. and Wu, D. and Ke, W. L.
CN-01259012	Zinc supplementation and the effects on metabolic status in gestational diabetes: a randomized, double-blind, placebo-controlled trial	2 0 1 5	Journal of diabetes and its complications	1873-460X	2 9	8 13 14 æ 01 31 9	Karamali, M. and Heidarzadeh, Z. and Seifati, S. M. and Samimi, M. and Tabassi, Z. and Hajjafari, M. and Asemi, Z. and Esmailzadeh, A.
109726672. Language: English. Entry Date: 20150923. Revision Date: 20160507. Publication Type: journal article	Intensive low-glycaemic-load dietary intervention for the management of glycaemia and serum lipids among women with gestational diabetes: a randomized control trial	2 0 1 5	Public Health Nutrition		1 8	8 15 06 - 15 13	Ma, Wen-Jun and Huang, Zhi-Hong and Huang, Bi-Xia and Qi, Ben-Hua and Zhang, Yan-Jun and Xiao, Ben-Xi and Li, Yuan-Hong and Chen, Li and Zhu, Hui-Lian
CN-01049846	A comparison between two oral hypoglycemics: glyburide and metformin and their combination for the treatment of gestational diabetes mellitus e a prospective randomized controlled study	2 0 1 5	American journal of obstetrics and gynecology	0002-9378 Y2 - 2010/03//	2 1 2	1 3å 00	Nachum, Z. and Zafran, N. and Salim, R. and Hissin, N. and Hasanein, J. and Ze Letova, Y. G. and Suleiman, A.
CN-01101288	Effect of an exercise intervention on gestational diabetes mellitus: a randomized controlled trial	2 0 1 5	Obstetrics and gynecology	1873-233X	1 2 5	5 11 95 æ 01 20 4	Nobles, C. and Marcus, B. H. and Stanek, E. J. and Braun, B. and Whitcomb, B. W. and Solomon, C. G. and Manson, J. E. and Markenson, G. and Chasan-Taber, L.
109784230. Language: English. Entry Date: 20150731. Revision Date: 20180823. Publication Type: journal article	Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials	2 0 1 5	Fertility & Sterility		1 0 3	5 12 78 - 12 88 e 4	PÁ@rez-LÁ³pez, Faustino R. and Pasupuleti, Vinay and Mezones-Holguin, Edward and Benites-Zapata, Vicente A. and Thota, Priyaleela and , Deshp and e, Abhishek and , Hern and ez, Adrian V.
CN-01435642	Sijunzi Tang, Astragalus Radix assisted with diet exercise therapy in treatment of gestational diabetes mellitus with deficiency of Qi and Yin type	2 0 1 5	Chinese journal of experimental traditional medical formulae [zhong guo shi yan fang ji xue za zhi]		2 1	2 1å 00 18 4	Xie, L. and Zhao, D. X. and Li, Z. Y. and Ma, J.
25925501	Metformin versus insulin for gestational diabetes mellitus: a meta-analysis	2 1 5	British Journal of Clinical Pharmacology		8 0	5 12 24 - 34	Zhao, L. P. and Sheng, X. Y. and Zhou, S. and Yang, T. and Ma, L. Y. and Zhou, Y. and Cui, Y. M.
WOS:000390757900005	TREATMENT OF GESTATIONAL DIABETES MELLITUS: INSULIN OR METFORMIN?	2 0 1 5	Journal of Evolution of Medical and Dental Sciences-Jemds	2278-4748	5 3	6 44 23 - 44 29	Somani, P. S. and Sahana, P. K. and Chaudhuri, P. and Sengupta, N.
WOS:000357039200004	Favorable Effects of Vitamin D Supplementation on Pregnancy Outcomes in Gestational Diabetes: A Double Blind Randomized Controlled Clinical Trial	2 0 1 5	Hormone and Metabolic Research	0018-5043	4 7	8 56 5- 57 0	Asemi, Z. and Karamali, M. and Esmailzadeh, A.
WOS:000348433700003	Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis	2 0 1 5	Bmj-British Medical Journal	1756-1833	3 5 0		Balsells, M. and Garcia-Patterson, A. and Sola, I. and Roque, M. and Gich, I. and Corcoy, R.
26241419	Glyburide in Women With Mild Gestational Diabetes: A Randomized Controlled Trial	2 0 1 5	Obstetrics & Gynecology		1 2 6	30 3- 9	Casey, B. M. and Duryea, E. L. and Abbassi-Ghanavati, M. and Tudela, C. M. and Shivers, S. A. and McIntire, D. D. and Leveno, K. J.
WOS:000361653200019	Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial	2 0 1 5	Lancet Diabetes & Endocrinology	2213-8587	3 0	1 77 8- 78 6	Chiswick, C. and Reynolds, R. M. and Denison, F. and Drake, A. J. and Forbes, S. and Newby, D. E. and Walker, B. R. and Quenby, S. and Wray, S. and Weeks, A. and Lashen, H. and Rodriguez, A. and Murray, G. and Whyte, S. and Norman, J. E.
WOS:000376206600006	COMPARISON OF METFORMIN WITH GLYBURIDE IN GESTATIONAL DIABETES: A DOUBLE BLIND RANDOMISED CLINICAL TRIAL	2 0 1 5	Journal of Evolution of Medical and Dental Sciences-Jemds	2278-4748	4 8	2 48 03 - 48 08	Fenn, M. G. and Isac, M. and George, M. and Korula, S.
WOS:000357942200018	Home-Based Exercise Improves Fitness and Exercise Attitude and Intention in Women with GDM	2 0 1 5	Medicine and Science in Sports and Exercise	0195-9131	4 7	8 16 98 - 17 04	Halse, R. E. and Wallman, K. E. and Dimmock, J. A. and Newham, J. P. and Gueffi, K. J.
WOS:000357669000064	Comparative Efficacy and Safety of OADs in Management of GDM: Network Meta-analysis of Randomized Controlled Trials	2 0 1 5	Journal of Clinical Endocrinology & Metabolism		1 0 0	5 20 71 - 20 80	Jiang, Y. F. and Chen, X. Y. and Ding, T. and Wang, X. F. and Zhu, Z. N. and Su, S. W.
WOS:000360906200018	Metformin for the treatment of gestational diabetes: An updated meta-analysis	2 0 1 5	Diabetes Research and Clinical Practice	0168-8227	1 0 9	3 52 1- 53 2	Kitwitee, P. and Limwattananon, S. and Limwattananon, C. and Waleekachonliert, O. and Ratanachotpanich, T. and Pimphilai, M. and Nguyen, T. V. and Pongchaiyakul, C.
WOS:000355657800016	Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs	2 0 1 5	Archives of Gynecology and Obstetrics		2 9 2	1 11 1- 12 0	Li, G. X. and Zhao, S. J. and Cui, S. H. and Li, L. and Xu, Y. J. and Li, Y. Y.

Appendix 2

WOS:000352147100021	Impact of probiotics in women with gestational diabetes mellitus on metabolic health: a randomized controlled trial	2 0 1 5	American Journal of Obstetrics and Gynecology	2 1 2	4 1 2	Lindsay, K. L. and Brennan, L. and Kennelly, M. A. and Maguire, O. C. and Smith, T. and Curran, S. and Coffey, M. and Foley, M. E. and Hatunic, M. and Shanahan, F. and McAuliffe, F. M.	
26287776	Effect of an Exercise Intervention on Gestational Diabetes Mellitus: A Randomized Controlled Trial	2 0 1 5	Obstetrics & Gynecology	1 2 6	3 6 6	Taghiof, H. and Rezaei, S. and Henderson, C. E.	
CN-01215349	Calcium plus vitamin D supplementation affects pregnancy outcomes in gestational diabetes: randomized, double-blind, placebo-controlled trial	2 0 1 6	Public health nutrition	1475-2727; 1368-9800	1 9 63	1 6 63	Karamali, M. and Asemi, Z. and Ahmadi-Dastjerdi, M. and Esmailzadeh, A.
rayyan-3785097	Short-term antidiabetic treatment with insulin or metformin has a similar impact on the components of metabolic syndrome in women with gestational diabetes mellitus requiring antidiabetic agents: results of a prospective, randomised study	2 0 1 6	Journal of physiology and pharmacology	6 7	2 7	22 7-23 3	Zawiejska, A. and Wender-Ozegowska, E. and Grewling-Szmit, K. and Brazert, M. and Brazert, J.
CN-01210646	Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes	2 0 1 6	Cochrane database of systematic reviews (online)	2 0 1 6	9 0 6	Brown, J. and Crawford, T. J. and Alsweller, J. and Crowther, C. A.	
CN-01193712	A phytosterol-enriched spread improves lipid profile and insulin resistance of women with gestational diabetes mellitus: a randomized, placebo-controlled double-blind clinical trial	2 0 1 6	Diabetes technology and therapeutics.	18 (8) (pp 499-504).	2016. Date of publication: august 2016.		
CN-01379362	The effects of synbiotic supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes: a randomised, double-blind, placebo-controlled trial	2 0 1 6	British journal of nutrition	1 1 6	8 13 94	13 94 94	Ahmadi, S. and Jamilian, M. and Tajabadi-Ebrahimi, M. and Jafari, P. and Asemi, Z.
CN-01177108	Use of a real time continuous glucose monitoring system as an educational tool for patients with gestational diabetes	2 0 1 6	Diabetology & metabolic syndrome	1758-5996	8 1	1	Alfadhli, E. and Osman, E. and Basri, T.
CN-01383169	Effect of Acupressure on Maternal Anxiety in Women With Gestational Diabetes Mellitus: a Randomized Clinical Trial	2 0 1 6	Clinical nursing research	1552-3799	2 5	3 32 58 34 1	Bastani, F.
WOS:000379488300001	Effects of a Multispecies Probiotic Mixture on Glycemic Control and Inflammatory Status in Women with Gestational Diabetes: A Randomized Controlled Clinical Trial	2 0 1 6	Journal of Nutrition and Metabolism	2090-0732			Jafarnejad, S. and Saremi, S. and Jafarnejad, F. and Arab, A.
CN-01444695	Vitamin D3-Supplemented Yogurt Drink Improves Insulin Resistance and Lipid Profiles in Women with Gestational Diabetes Mellitus: a Randomized Double Blinded Clinical Trial	2 0 1 6	Annals of nutrition & metabolism	1421-9697	6 8	4 28 58 29 0	Li, Q. and Xing, B.
CN-01459500	Comparing twice- versus four-times daily insulin in mothers with gestational diabetes in Pakistan and its implications	2 0 1 6	Journal of comparative effectiveness research	2042-6313	5 5	5 45 38 45 9	Saleem, N. and Godman, B. and Hussain, S.
CN-01292154	Artemisia Extract Improves Insulin Sensitivity in Women With Gestational Diabetes Mellitus by Up-Regulating Adiponectin	2 0 1 6	Journal of clinical pharmacology	5 6	1 2	15 50 8 11 55 4	Sun, X. and Sun, H. and Zhang, J. and Ji, X.
113826493. Language: English. Entry Date: 20160725. Revision Date: 20160725. Publication Type: Article	Capsaicin-containing chili improved postprandial hyperglycemia, hyperinsulinemia, and fasting lipid disorders in women with gestational diabetes mellitus and lowered the incidence of large-for-gestational-age newborns	2 0 1 6	Clinical Nutrition	3 5	2 8	38 8-39 3	Yuan, Li-Jia and Qin, Yu and Wang, Lin and Zeng, Yuan and Chang, Hui and Wang, Jian and Wang, Bin and Wan, Jing and Chen, Shi-Hui and Zhang, Qian-Yong and Zhu, Jun-Dong and Zhou, Yong and Mi, Man-Tian
WOS:000379847000007	Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus	2 0 1 6	Journal of Obstetrics and Gynaecology Research	4 2	6 6	64 0-64 7	Ashoush, S. and El-Said, M. and Fathi, H. and Abdelnaby, M.
WOS:000399001400011	Comparison of Glibenclamide and Insulin on Neonatal Outcomes in Pregnant Women with Gestational Diabetes	2 0 1 6	International Journal of Preventive Medicine	2008-7802-2008-8213 (electronic)	7		Behrashi, M. and Samimi, M. and Ghasemi, T. and Saberi, F. and Atoof, F.
WOS:000384788000006	A Randomized Clinical Trial of an Intensive Behavior Education Program in Gestational Diabetes Mellitus Women Designed to Improve Glucose Levels on the 2-Hour Oral Glucose Tolerance Test	2 0 1 6	American Journal of Perinatology	0735-1631	3 3	1 2 11 51	Durnwald, C. P. and Kallan, M. J. and Allison, K. C. and Sammel, M. D. and Wisch, S. and Elovitz, M. and Parry, S.
27526637	Efficacy of Internet-Based Self-Monitoring Interventions on Maternal and Neonatal Outcomes in Perinatal Diabetic Women: A Systematic Review and Meta-Analysis	2 0 1 6	Journal of Medical Internet Research	1 8	8 8	e2 20	Lau, Y. and Htun, T. P. and Wong, S. N. and Tam, W. S. and Klainin-Yobas, P.
27258511	Effects of Low Glycemic Index Diets on Gestational Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Clinical Trials	2 0 1 6	Medicine	9 5	2 2	e3 79 2	Wei, J. and Heng, W. and Gao, J.
WOS:000368673000001	Effect of a CGMS and SMBG on Maternal and Neonatal Outcomes in Gestational Diabetes Mellitus: a Randomized Controlled Trial	2 0 1 6	Scientific Reports	2045-2322	6		Wei, Q. and Sun, Z. L. and Yang, Y. and Yu, H. and Ding, H. J. and Wang, S. H.
WOS:000377050700011	Effects of vitamin D supplementation on metabolic indices and hs-CRP levels in gestational diabetes mellitus patients: a randomized, double-blinded, placebo-controlled clinical trial	2 0 1 6	Nutrition Research and Practice	1976-1457	1 0	3 8-33 5	Yazdchi, R. and Gargari, B. P. and Asghari-Jafarabadi, M. and Sahhaf, F.

Appendix 2

WOS:000374576100016	Metformin versus insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials	2 0 1 6	Irish Journal of Medical Science		1 8 5	2 2 5	37 1- 38 1	Zhu, B. and Zhang, L. and Fan, Y. Y. and Wang, L. and Li, X. G. and Liu, T. and Cao, Y. S. and Zhao, Z. G.
12031426. Language: English. Entry Date: 20161220. Revision Date: 20180706. Publication Type: Article	Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis	2 0 1 7	Diabetic Medicine	0742-3071	3 4	1 4	27 - 36	Butalia, S. and Gutierrez, L. and Lodha, A. and Aitken, E. and Zakariassen, A. and Donovan, L.
CN-01643586	Phytosterol nutritional supplement improves pregnancy and neonatal complications of gestational diabetes mellitus in a double-blind and placebo-controlled clinical study	2 0 1 7	Food & function	2042-650X	8	1	42 48 42 8	Gao, F. and Wang, G. and Wang, L. and Guo, N.
123013241. Language: English. Entry Date: 20170605. Revision Date: 20180309. Publication Type: Article	The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes	2 0 1 7	Journal of Clinical Lipidology		1 1	2 45	45 9- 46 8	Jamilian, Mehri and Samimi, Mansooreh and Ebrahimi, Faraneh Afshar and Hashemi, Teibeh and Taghizadeh, Mohsen and Razavi, Maryamsadat and Sanami, Marzieh and Asemi, Zatollah
CN-01400876	Gestational Diabetes Mellitus and Frequency of Blood Glucose Monitoring: a Randomized Controlled Trial	2 0 1 7	Obstetrics and gynecology	1873-233X	1 3 0	1 3	16 38 42 0	Mendez-Figueroa, H. and Schuster, M. and Maggio, L. and Pedroza, C. and Chauhan, S. P. and Paglia, M. J.
121395474. Language: English. Entry Date: 20171021. Revision Date: 20180428. Publication Type: journal article	Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study	2 0 1 7	Diabetes Care		4 0	3 2- 33 7	33 2- 33 7	Nachum, Zohar and Zafran, Noah and Salim, Raed and Hissin, Noura and Hasanein, Jamal and Ze Letova, Yifat Gam and Suleiman, Abeer and Yefet, Enav and Gam Ze Letova, Yifat
123241474. Language: English. Entry Date: 20180117. Revision Date: 20190102. Publication Type: Article	Effect of Probiotics on Metabolic Outcomes in Pregnant Women with Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	2 0 1 7	Nutrients		9	5	46 1	Taylor, Bonnie L. and Woodfall, Georgia E. and Sheedy, Katherine E. and O'Riley, Meggan L. and Rainbow, Kelsie A. and Bramwell, Elsa L. and Kellow, Nicole J.
CN-01430963	The comparison of the safety and effectiveness of multiple insulin injections and insulin pump therapy in treating gestational diabetes	2 0 1 7	Biomedical research (india)		3 8	2 8	1 8 30 3 83 3	Xie, J. and Dai, L. and Tang, X.
29103210	Insulin for the treatment of women with gestational diabetes	2 0 1 7	Cochrane Database of Systematic Reviews		1 1		C D 01 20 37	Brown, J. and Grzeskowiak, L. and Williamson, K. and Downie, M. R. and Crowther, C. A.
28120427	Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes	2 0 1 7	Cochrane Database of Systematic Reviews		1		C D 01 19 67	Brown, J. and Martis, R. and Hughes, B. and Rowan, J. and Crowther, C. A.
28930827	Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus: An updated PRISMA-compliant network meta-analysis	2 0 1 7	Medicine		9 6	3 8	e7 93 9	Liang, H. L. and Ma, S. J. and Xiao, Y. N. and Tan, H. Z.
WOS:000416095500026	Feto-maternal outcomes and Glycemic control in Metformin versus insulin treated Gestational Diabetics	2 0 1 7	Pakistan Journal of Medical Sciences		3 3	5	11 - 11 87	Arshad, R. and Khanam, S. and Shaikh, F. and Karim, N.
28472859	Lifestyle interventions for the treatment of women with gestational diabetes	2 0 1 7	Cochrane Database of Systematic Reviews		5		C D 01 19 70	Brown, J. and Alwan, N. A. and West, J. and Brown, S. and McKinlay, C. J. and Farrar, D. and Crowther, C. A.
WOS:000408592100014	Effect of Probiotic Supplementation on Blood Pressure of Females with Gestational Diabetes Mellitus: A Randomized Double Blind Controlled Clinical Trial	2 0 1 7	Iranian Red Crescent Medical Journal		1 9	6		Hajifaraji, M. and Jahanjou, F. and Abbasalizadeh, F. and Aghamohammadzadeh, N. and Abbasi, M. M. and Dolatkah, N.
WOS:000424557100027	Metformin versus Insulin Treatment in Gestational Diabetes in Pregnancy and Their Effects on Neonatal Birthweight	2 0 1 7	Pakistan Journal of Medical & Health Sciences	1996-7195	1 1	3	91 4- 91 6	Hamadani, A. and Zahid, S. and Butt, Z. B.
WOS:000411759200002	Glibenclamide and metformin versus standard care in gestational diabetes (GRACES): a feasibility open label randomised trial	2 0 1 7	Bmc Pregnancy and Childbirth	1471-2393	1 7			Reynolds, R. M. and Denison, F. C. and Juszcak, E. and Bell, J. L. and Penneycard, J. and Strachan, M. W. J. and Lindsay, R. S. and Alex and er, C. I. and Love, C. D. B. and Whyte, S. and Mackenzie, F. and Stenson, B. and Norman, J. E.
WOS:000410794100005	Randomized controlled trial of induction at 38 weeks versus 40 weeks gestation on maternal and infant outcomes in women with insulin-controlled gestational diabetes	2 0 1 7	Wiener Klinische Wochenschrift		1 2 9	1 7	61 8- 62 4	Worda, K. and Bancher-Todesca, D. and Husslein, P. and Worda, C. and Leipold, H.
WOS:000400381900024	Effectiveness of cognitive-behavioral stress management on psychological stress and glycemic control in gestational diabetes: a randomized controlled trial	2 0 1 7	Journal of Maternal-Fetal & Neonatal Medicine	1476-7058	3 0	1 1	13 78 - 13 82	Zaheri, H. and Najar, S. and Abbaspoor, Z.
WOS:000400767700015	Sitagliptin down-regulates retinol-binding protein 4 and reduces insulin resistance in gestational diabetes mellitus: a randomized and double-blind trial	2 0 1 7	Metabolic Brain Disease	0885-7490	3 2	3	77 3- 77 8	Sun, X. and Zhang, Z. D. and Ning, H. and Sun, H. and Ji, X. H.
WOS:000408590600022	Effect of Educational Package on Self-care Behavior, Quality of Life, and Blood Glucose Levels in Pregnant Women with	2 0	Iranian Red Crescent Medical Journal		1 9	4		, Z and inava, H. and Shafaei, F. S. and , Char and abi, S. M. A. and Homayi, S. G. and , Mirghafour and , M.

Appendix 2

	Gestational Diabetes: A Randomized Controlled Trial	1 7							
130526634.	Medical nutrition treatment of women with gestational diabetes mellitus by a telemedicine system based on smartphones	2 0 1 8	Journal of Obstetrics & Gynaecology Research	- 1615 2	4 4 2	7 12 28 12 34		Yang, Ping and Lo, Wenpin and He, Zongâ€¦lin and Xiao, Xiaohâ€¦min	
Language: English.									
Entry Date: 20180710.									
Revision Date: 20180713.									
Publication Type: Article									
CN-01618957	Ameliorative potential of acupuncture on gestational diabetes mellitus: a randomized controlled trial	2 0 1 8	Journal of complementary and integrative medicine	Suppl				El-Shamy, F. F. and El-Kholy, S. S. and Labib, M. and Kabel, A. M.	
CN-01655653	The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes	2 0 1 8	Lipids in health and disease	1476-511X	1 7	1 3	16	Maktabi, M. and Jamilian, M. and Amirani, E. and Chamani, M. and Asemi, Z.	
CN-01450770	A randomized control trial on the effect of introducing a daily smartphone based feedback system between GDM patients and physicians on patient compliance, glycemic control, satisfaction, and pregnancy outcome	2 0 1 8	American journal of obstetrics and gynecology	0002-9378 Y2 - 2010 /03//	2 1 8	1 1â€¦ â€¦	53	Miremberg, H. and Ben-Ari, T. and Betzer, T. and Raphaeli, H. and Gasnier, R. and Barda, G. and Bar, J. and Weiner, E.	
CN-01647130	Randomised controlled trial of very tight versus less tight glycaemic targets in women with gestational diabetes: preliminary results	2 0 1 8	Diabetologia	0012-186X	6 1		52 7â€¦ â€¦ 52 8	Popova, P. and Tkachuck, A. and Bolotko, Y. and Gerasimov, A. and Pustozero, E. and Vasilyeva, E. and Li, O. and Zazerskaya, I. and Grineva, E.	
CN-01367757	Effect of oral protein hydrolysate on glucose control in patients with gestational diabetes	2 0 1 8	Clinical nutrition (edinburgh, scotland)		3 7	3	87 8â€¦ â€¦ 88 3	Saleh, L. and Schrier, N. L. and Bruins, M. J. and Steegers, E. A. P. and van den Meiracker, A. H. and Visser, W.	
129438601.	Effect of Glyburide vs Subcutaneous Insulin on Perinatal Complications Among Women With Gestational Diabetes: A Randomized Clinical Trial	2 0 1 8	JAMA: Journal of the American Medical Association	0098-7484 Print	3 1 9	1 7	17 73 17 80	SÃ©nat, Marie-Victoire and Affres, Helene and Letourneau, Alex and , ra and Coustols-Valat, Magali and Cazaubiel, Marie and Legardeur, Helene and Jacquier, Julie Fort and Bourcigaux, Nathalie and Simon, Emmanuel and Rod, Anne and HÃ©ron, Isabelle and Castera, Virginie and Sentilhes, Loic and Bretelle, Florence and , Roll and , Catherine and Morin, Mathieu and Deruelle, Philippe and De Carne, Celine and Maillot, FranÃ§ois and Beucher, Gael	
Language: English.									
Entry Date: 20180512.									
Revision Date: 20190108.									
Publication Type: Journal article									
CN-01643329	Combination of a structured aerobic and resistance exercise improves glycaemic control in pregnant women diagnosed with gestational diabetes mellitus. A randomised controlled trial	2 0 1 8	Women and birth		3 1	3 4	e2 32 â€¦ â€¦ 23 8	Sklempe Kokic, I. and Ivanisevic, M. and Biolo, G. and Simunic, B. and Kokic, T. and Pisot, R.	
CN-01667542	Lifestyle intervention in Danish obese pregnant women with early gestational diabetes mellitus according to WHO 2013 criteria does not change pregnancy outcomes: results from the LIP (Lifestyle in Pregnancy) study	2 0 1 8	Diabetes care	0149-5992	4 1	1 0	20 79 â€¦ â€¦ 08 5	Vinter, C. A. and Tanvig, M. H. and Christensen, M. H. and Ovesen, P. G. and Jorgensen, J. S. and Andersen, M. S. and McIntyre, H. D. and Jensen, D. M.	
30103263	Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews	2 0 1 8	Cochrane Database of Systematic Reviews		8		C D 01 23 27	Martis, R. and Crowther, C. A. and Shepherd, E. and Alswelner, J. and Downie, M. R. and Brown, J.	
WOS:000428406300022	The impact of a daily smartphone-based feedback system among women with gestational diabetes on compliance, glycemic control, satisfaction, and pregnancy outcome: a randomized controlled trial	2 0 1 8	American Journal of Obstetrics and Gynecology		2 1 8	4 7	7	Miremberg, H. and Ben-Ari, T. and Betzer, T. and Raphaeli, H. and Gasnier, R. and Barda, G. and Bar, J. and Weiner, E.	
WOS:000437670900005	Effect of inositol stereoisomers at different dosages in gestational diabetes: an open-label, parallel, randomized controlled trial	2 0 1 8	Acta Diabetologica	0940-5429;	5 5	8	80 5- 81 2	Fratlicelli, F. and Celentano, C. and Zecca, I. A. L. and Di Vieste, G. and Pintaudi, B. and Liberati, M. and Franzago, M. and Di Nicola, M. and Vitacolonna, E.	
WOS:000426464400005	Lifestyle interventions for gestational diabetes mellitus to control blood glucose: a meta-analysis of randomized studies	2 0 1 8	International Journal of Diabetes in Developing Countries		3 8	1	26 - 35	Guo, W. W. and Zhang, B. H. and Wang, X.	
WOS:000432567000012	Effect of probiotic supplements in women with gestational diabetes mellitus on inflammation and oxidative stress biomarkers: a randomized clinical trial	2 0 1 8	Asia Pacific Journal of Clinical Nutrition	0964-7058;	2 7	3	58 1- 59 1	Hajifaraji, M. and Jahanjou, F. and Abbasalizadeh, F. and Aghamohammadzadeh, N. and Mesgari, M. and Dolatkah, N.	
WOS:000435926000019	A Tailored Letter Based on Electronic Health Record Data Improves Gestational Weight Gain Among Women With Gestational Diabetes Mellitus: The Gestational Diabetes' Effects on Moms (GEM) Cluster-Randomized Controlled Trial	2 0 1 8	Diabetes Care		4 1	7	13 70 - 13 77	Hedderson, M. M. and Brown, S. D. and Ehrlich, S. F. and Tsai, A. L. and Zhu, Y. Y. and Quesenberry, C. P. and Crites, Y. and Ferrara, A.	
WOS:000452704800002	Amino acid profile in women with gestational diabetes mellitus treated with metformin or insulin	2 0 1 8	Diabetes Research and Clinical Practice	0168-8227	1 4 6		Au g- 17	Huhtala, M. S. and Tertti, K. and Pellonpera, O. and Ronnema, T.	
WOS:000430445500019	The effects of synbiotic supplementation on insulin resistance/sensitivity, lipid profile and total antioxidant capacity in women with gestational diabetes mellitus: A randomized double blind placebo controlled clinical trial	2 0 1 8	Diabetes Research and Clinical Practice	0168-8227	1 3 8		14 9- 15 7	Nabhani, Z. and Hezaveh, S. J. G. and Razmpoosh, E. and Asghari-Jafarabadi, M. and Gargari, B. P.	
WOS:000440297500031	Using technology to support care in gestational diabetes mellitus: Quantitative outcomes of an exploratory randomised control trial of adjunct telemedicine for gestational diabetes mellitus (TeleGDM)	2 0 1 8	Diabetes Research and Clinical Practice	0168-8227	1 4 2		27 6- 28 5	Rasekaba, T. M. and Furler, J. and Young, D. and Liew, D. and Gray, K. and Blackberry, I. and Lim, W. K.	
WOS:000431908200003	The treatment of booking gestational diabetes mellitus (TOBOGDM) pilot randomised controlled trial	2 0 1 8	Bmc Pregnancy and Childbirth	1471-2393	1 8			Simmons, D. and Nema, J. and Parton, C. and Vizza, L. and Robertson, A. and Rajagopal, R. and Ussher, J. and Perz, J.	
WOS:000454621900021	Detection and initial management of gestational diabetes through primary	2 0	Plos One	1932-6203	1 3	1 2		Utz, B. and Assarag, B. and Smekens, T. and Ennassiri, H. and Lekhal, T. and El Ansari, N. and Fakhir, B. and Barkat, A. and Essolbi, A. and De Brouwere, V.	

Appendix 2

	health care services in Morocco: An effectiveness-implementation trial	1 8					
WOS:0004383405 00011	Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial	2 0 1 8	Diabetes Obesity & Metabolism	1462- 8902	2 0	8 18 94 - 19 02	Voormolen, D. N. and DeVries, J. H. and Sanson, R. M. E. and Heringa, M. P. and de Valk, H. W. and Kok, M. and van Loon, A. J. and Hoogenberg, K. and Bekedam, D. J. and Brouwer, T. C. B. and Porath, M. and Erdtsieck, R. J. and NijBijvank, B. and Kip, H. and van der Heijden, O. W. H. and Elving, L. D. and Hermesen, B. B. and van Loon, B. J. P. and Rijnders, R. J. P. and Jansen, H. J. and Langenveld, J. and Akerboom, B. M. C. and Kiewiet, R. M. and Naaktgeboren, C. A. and Mol, B. W. J. and Franx, A. and Evers, I. M.

Appendix 3

Appendix 3 License Statement for Paper 1 (Developing a core outcome set for the treatment of pregnant women with pregestational diabetes—a study protocol)

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Appendix 4

Appendix 4 License Statement for Paper 4 (A Core Outcome Set for Studies of Gestational Diabetes Mellitus Prevention and Treatment)

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Appendix 5 License Statement for Paper 5 (Core Outcome Sets for Studies of Diabetes in Pregnancy: A Review)

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