PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and acceptability of metformin in preventing onset of type 2 diabetes after gestational diabetes in postnatal women: a protocol for a randomised, placebo-controlled, double-blind feasibility trial Optimising health outcomes with Metformin to prevent diAbetes After pregnancy (OMAhA)
AUTHORS	Amaefule, Chiamaka; Bolou, Angeliki; Drymoussi, Zoe; Gonzalez Carreras, Francisco; Pardo Llorente, Maria del Carmen; Lanz, Doris; Dodds, Julie; Sweeney, Lorna; Pizzo, Elena; D'Amico, Maria; Thomas, Amy; Heighway, James; Daru, Jahnavi; Sobhy, Soha; Robson, John; Sanghi, Anita; Zamora, Javier; Harden, Angela; Hitman, Graham; Khan, Khalid; Pérez, Teresa; Huda, Mohammed; Thangaratinam, Shakila

VERSION 1 – REVIEW

REVIEWER	David A Sacks Kaiser Permanente Southern California
REVIEW RETURNED	24-Dec-2019

GENERAL COMMENTS	The authors present a proposal for a blinded randomized placebo controlled feasibility trial of metformin shortly following delivery of a pregnancy complicated by insulin- or metformin-requiring gestational diabetes. Page 15: Under "Strengths and limitations of this study" please clarify which of the 4 items the authors deem strengths and which limitations. Page 17 line 16: Do the authors also wish to determine the healthcare professionals' perceptions of risks and benefits of metformin? Page 17 Line 18: The authors imply that pre-diabetes is a different category from IFG or IGT (c.f. following comment). Please clarify. Page 18 Table 1: Please provide page references for the citations in the third column. This reviewer was unable to find a WHO or NICE diagnosis of IGT that included reference to fasting glucose. In contrast, the American Diabetes Association defines IGT as a 2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)(IGT) and prediabetes as IGT or FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG) or A1C 5.7–6.4% (39–47 mmol/mol). Please clarify these definitions. Page 19: The authors plan on studying only those women who during pregnancy required pharmacological treatment in addition to diet. Please explain why this limitation is imposed. Page 19: Among the exclusion criteria do the authors also wish to add any or all of those with stillbirths, neonatal deaths, preterm deliveries, cesarean deliveries, or multiple gestations?

	Page 20, line 4: Please consider comparing the demographics of those who are eligible and agree to participate in the study with those who disagree to participate in the study, to assure that the data obtained is representative of the population from which the sample was derived. Page 21 line 11: Please clarify at what time relative to childbirth the metformin or placebo will be initiated. Page 21: Intervention and control arms: The authors state that patients will receive 500 mg sustained release (SR) metformin pills in progressive doses to 2 grams/day. Given that the time to peak of metformin SR is 4-8 hours, it seems likely that, even with a 1000 mg bid dosing, there will be overlap of the metformin levels in patients' blood. Is that a concern? Also, to maintain blinding, how will placebo be dosed incrementally? Finally, will patients receive any supervised or unsupervised diet and exercise instruction? Page 22, line 5-6: How will women's views of the recruitment process and of the risk of type 2 be assessed? Page 22, line 8: It also seems relevant to report the time from initiation of the study that women who dropped out did so, and the dose of metformin or placebo that they were taking at that time. Page 22, line 11: The duration and frequency of breastfeeding should also be documented. Page 22, line 13: When the authors state that they will measure 2-hour glucose, do they mean to assess glucose two hours after the first bite of a meal or 2-hours after ingestion of 75g glucose for a glucose tolerance test, or something else? Page 23 line 1: Will these follow-up visits be conducted in the office? Using video? By phone? Page 23, lines 8-9: Please clarify how women found to have pre-diabetes or diabetes at 6-13 weeks or 6 months will be treated. Page 24, line 2: Please briefly describe what standard practice for follow-up care consists of. Page 24, Sample Size: Please state the total annual delivery rate at the participating institutions, the prevalence of gestational diabetes (GDM) at each institution, and the rate of addition of pharma treatment among the women with GDM. Page 31, lines 13-15: The sentence, "to encourage adherence…to take the intervention." should first be mentioned in the Methods.

REVIEWER	Christina Scifres Indiana University School of Medicine
REVIEW RETURNED	05-Jan-2020

GENERAL COMMENTS	Thank you for the opportunity to review the article by Amaefule, et al. entitled "Effectiveness and acceptability of metformin in preventing onset of type 2 diabetes after gestational diabetes in postnatal women: a protocol for a randomized, placebo-controlled, double-blind feasibility trial." This is a protocol paper for the OMAhA study, which will evaluate the feasibility of metformin in the immediate postpartum period to prevent type 2 diabetes among women with a history of GDM. This protocol paper is well-written, and this feasibility study addresses an important public health concern. I would like to make the following comments: 1. In the introduction, the authors state that the "Diabetes Prevention Programme demonstrated that the reduction in type 2 diabetes risk persisted 10 years after commencing metformin after women with gestational diabetes (page 5; lines 29-33)." While I agree with this statement, it would be worth mentioning that all the women with a history of GDM enrolled in the DPP had evidence of impaired glucose tolerance. One novel aspect of the proposed

	study is that it will involve a broader population of women with GDM, and not just those who already have evidence of impaired glucose tolerance. 2. Will the results of the 6-13 week and 1-year oral glucose tolerance test be blinded to patients enrolled in the study and their usual care providers? If the results will be blinded, under what circumstances will they be revealed to patients and providers? If not blinded, how will the authors safeguard against other interventions being undertaken in clinical care that might influence the study outcomes (i.e. use of other medications to reduce the risk for type 2 diabetes, tailored lifestyle counseling, ect?) 3. How will women who test positive for type 2 diabetes at the 6-13-week visit be managed? Although rare, it is possible that some women who required medical therapy for their GDM will be diagnosed with type 2 diabetes in the immediate postpartum period. Typical standards of care would call for these women to be started on metformin, so it would be helpful if the authors provided additional information about their approach to this subset of women. 4. For the sample size calculations (page 13, line 19) the authors state that they expect at least 1000 women diagnosed with GDM annually are eligible for participation. Can they provide additional information on the total number of deliveries at enrolling hospitals, percent of women with GDM, and percent of women with GDM who are treated with metformin or insulin? This would be very helpful to the reader's understanding of the patient population. 5. How will participants be selected for the quantitative interviews? 6. Page 12, line 36-38 states that maternal and infant outcomes will also be collected as outlined in Figure 1. However, figure 1 only states that maternal and baby outcomes will be collected. It would be helpful if the authors provided more specific information about the outcomes that they will be collecting.

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer's comments

Reviewers' Comments	**Authors' Response**
Reviewer #1	
Page 15: Under "Strengths and limitations of this study", please clarify which of the 4 items the authors deem strengths and which limitations.	**Page 4**: The design of the trial in terms of being pragmatic, having a nested qualitative and economic evaluation and being double blinded are its strengths. The exclusion of participants who cannot provide informed consent in English Language can be deemed as a limitation, as this group may include minority ethnic groups who are most at risk for type 2 diabetes and can potentially benefit from the trial. The manuscript has been edited to ensure this is clear. See *"Page 4"*, *"Line 4 -14"*
Page 17 line 16: Do the authors also wish to determine the healthcare	

professionals' perceptions of risks and benefits of metformin?	**Page 6**: During the qualitative interviews with clinicians, their general perceptions of the intervention and trial and its potential role in routine practice will be discussed. This may include their perception of metformin as a preventative measure for type 2 diabetes. The manuscript has been edited to reflect the above. See *"Page 6"*, *"Line 22"*
Page 17 Line 18: The authors imply that pre-diabetes is a different category from IFG or IGT (c.f. following comment). Please clarify.	**Page 7:** Yes, we agree that pre-diabetes encompasses impaired fasting glucose, impaired glucose tolerance, and is not a separate entity. We were only listing all possible definitions. However, we have edited the manuscript to ensure this is clear. See "*Page 7", "Line "2-3".*
Page 18 Table 1: Please provide page references for the citations in the third column. This reviewer was unable to find a WHO or NICE diagnosis of IGT that included reference to fasting glucose. In contrast, the American Diabetes Association defines IGT as a 2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)(IGT) and prediabetes as IGT or FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG) or A1C 5.7–6.4% (39–47 mmol/mol). Please clarify these definitions.	**Page 7 Table 1:** The NICE guidance is the NICE Public Health guideline (PH38) which in line with WHO diagnostic criteria defines Impaired Glucose Tolerance as follows; *Impaired glucose tolerance; This is a risk factor for future diabetes and/or other adverse outcomes. The current WHO diagnostic criteria for impaired glucose tolerance are: a fasting plasma glucose of less than 7.0 mmol/l and a 2-hour venous plasma glucose (after ingestion of 75 g oral glucose load) of 7.8 mmol/l or greater, and less than 11.1 mmol/l.* The reference including link to the above is*:* National Institute for Health and Care Excellence. Type 2 Diabetes: prevention in people at high risk, Public Health guideline [PH38] Web site. https://www.nice.org.uk/guidance/ph38/chapter/Glossary Published July 2012. Last updated September 2017. Accessed 29th January, 2020.
Page 19: The authors plan on studying only those women who during pregnancy required pharmacological treatment in addition to diet. Please explain why this limitation is imposed.	The ADA guidelines have not been used in this context, as they do not reflect current UK clinical practice. The manuscript has also been edited to include references to the definitions of each form of maternal dysglycaemia. See *"Page 7"*, *"Table 1".*

	Page 8: Our focus on women with GDM on pharmacological treatment was informed by our meta-analysis, which showed an increased risk of progression to Type 2 diabetes in women with GDM who during pregnancy was managed with insulin. (Rayanagoudar, G., et al. 2016. Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. Diabetologia, 59(7), pp.1403-1411.).
Page 19: Among the exclusion criteria, do the authors also wish to add any or all of those with stillbirths, neonatal deaths, preterm deliveries, cesarean deliveries, or multiple gestations?	A systematic review also showed the beneficial role of pharmacological interventions in reducing the incidence of type 2 diabetes in this cohort. (Morton, S., et al., 2014. Interventions to modify the progression to type 2 diabetes mellitus in women with gestational diabetes: a systematic review of literature. Current Opinion in Obstetrics and Gynecology, 26(6), pp.476-486).
Page 20, line 4: Please consider comparing the demographics of those who are eligible and agree to participate in the study with those who disagree to participate in the study, to assure that the data obtained is representative of the population from which the sample was derived.	The manuscript have been edited to include the above. See *"Page 5", "Line 4-5"* and *"Line 19-20".*
Page 21 line 11: Please clarify at what time relative to childbirth the metformin or placebo will be initiated.	**Page 8:** Based on the eligibility criteria, women who are eligible regardless of having any of these delivery outcomes will be asked to confirm their willingness to continue with the trial. If they are willing, consent will be obtained and the participants will be randomised. However, we are aware of the psychological implications from having a still birth or neonatal death, but from our experience, women within this category are happy to continue with the trial.
Page 21: Intervention and control arms: The authors state that patients will receive 500 mg sustained release (SR) metformin pills in progressive doses to 2 grams/day. Given that the time to peak of metformin SR is 4-8 hours, it seems likely that, even with a 1000 mg bid dosing, there will be overlap of the metformin levels in patients' blood. Is that a concern? Also, to maintain blinding, how will placebo be dosed	**Page 9, line 4:** We thank the reviewer for this suggestion, which will be taken into consideration.

incrementally? Finally, will patients receive any supervised or unsupervised diet and exercise instruction?	
Page 22, line 5-6: How will women's views of the recruitment process and of the risk of type 2 be assessed?	**Page 10 line 11:** Randomised participants will receive the intervention after childbirth, before postnatal discharge and are advised to commence the trial medication just after discharge. Follow-up procedures include contacting participants within a week of discharge to ensure/encourage the immediate commencement of the medication. The manuscript has been edited to ensure this is clear. See *"Page 10"*, "*Line 15-16"* under the section titled *"Intervention and control arms"*. Also, see *"Page 12"*, *"Line 12-14"* under section *"Follow-up visits and outcome assessment"*.
Page 22, line 8: It also seems relevant to report the time from initiation of the study that women who dropped out did so, and the dose of metformin or placebo that they were taking at that time. **Page 22, line 11**: The duration and frequency of breastfeeding should also be documented. **Page 22, line 13**: When the authors state that they will measure 2-hour glucose, do they mean to assess glucose two hours after the first bite of a meal or 2-hours after ingestion of 75g glucose for a glucose tolerance test, or something else? **Page 23 line 1**: Will these follow-up visits be conducted in the office? Using video? By phone?	**Page 10:** a) Twice daily dosing is not a concern and we are not aware of harm from the overlap suggested. Twice daily dosing of Slow Release preparations is used commonly in clinical practice, as it aids compliance with large tablets, and is stated as acceptable within the Summary of Product Characteristics (SmPC). b) All trial participants will be contacted by research midwives to increase the dose of their trial medication accordingly. The research midwives are blinded to treatment allocations so all participants are treated the same way. We have edited the manuscript accordingly to ensure this is clear. See "*Page 10", Line 21-23* under the section titled *"Intervention and control arms*" on what the titration process entails as well as *"Line 5"* under the section on *"Blinding",.* c) Participants might receive diet and exercise instructions as part of routine practice, and this applies to all participants at all sites, independent of the trial or treatment allocation. However, diet and exercise advice is not an element of the trial intervention. See *Page 10*, for the section *"Intervention and Control arms"* on the elements of the trial intervention

Page 23, lines 8-9: Please clarify how women found to have pre-diabetes or diabetes at 6-13 weeks or 6 months will be treated.	**Page 11, line 12-13:** The qualitative interviews will involve discussions on women's perception of their risk for Type 2 diabetes. Their views of the recruitment process to assess acceptability will also be discussed. Thematic analysis of interview data will be used to identify and collate common views relating to these questions. See *"Page 14"*, *"Line 15-21"* for the objectives of the qualitative interviews. Also, see *"Page 15"*, *"Line 7-12"*on how the interview data will be analysed.
Page 24, line 2: Please briefly describe what standard practice for follow-up care consists of.	**Page 11, line 8:** We thank the reviewer for this suggestion, which will be explored as much as feasible.
	Page 12, line 1: We thank the reviewer for this comment, which will be explored as far as possible.
	Page 11, line 20: We mean we will measure participants' glucose levels, 2 hours after the ingestion of the 75g glucose drink during the Oral Glucose Tolerance Test. (OGTT). The manuscript has been revised to make sure this is clear. See *"Page 11"*, *"Line 20".*
	Page 12 line 11: The follow-up visits will be conducted primarily in person and if the participant is unavailable, by phone. We have edited the manuscript accordingly to include this. See *"Page "12"*, *"Line "11-12"* beneath the section titled "*Follow-up visits and outcome assessments*",
Page 24, Sample Size: Please state the total annual delivery rate at the participating institutions, the prevalence of gestational diabetes (GDM) at each institution, and the rate of addition of	**Page 13, l5-19:** Women found to have pre-diabetes will stay on the trial. However, women diagnosed with diabetes will be withdrawn from the trial and transferred

pharma treatment among the women with GDM. **Page 31, lines 13-15**: The sentence, "to encourage adherence…to take the intervention." should first be mentioned in the Methods.	to primary care for further treatment. In this event, if women provide consent, their General Practitioner (GP) is notified of their diagnosis. Upon request, the GP is notified of their treatment allocation to inform further treatment decision. We have edited the manuscript accordingly to include this. See *"Page 13",* the section titled "*Withdrawal criteria*", "*Line 5-9*" **Page 11, line 3:** Based on the NICE guideline, standard post-natal care for women diagnosed with gestational diabetes involve the following; For women who were diagnosed with gestational diabetes and whose blood glucose levels returned to normal after the birth: • Offer lifestyle advice (including weight control, diet and exercise). • Offer a fasting plasma glucose test 6–13 weeks after the birth to exclude diabetes.: • Advise women with a fasting plasma glucose level below 6.0 mmol/litre that: o they have a low probability of having diabetes at present o they should continue to follow the lifestyle advice (including weight control, diet and exercise) given after the birth o they will need an annual test to check that their blood glucose levels are normal • Advise women with a fasting plasma glucose level between 6.0 and 6.9 mmol/litre that they are at high risk of developing type 2 diabetes, and offer them advice, guidance and interventions in line with the NICE guideline on preventing type 2 diabetes. See link below for specific details; https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2

	The manuscript has been edited to include a summary of the above. See *"Page 11"*, *"Line 3-4".* **Page 13, Sample Size**: Based on a trust wide audit in 2017, see the below: <u>Annual delivery rate:</u> Royal London Hospital – 6500 Whipps Cross University Hospital – 5,500 Newham University Hospital – 7,000 <u>Prevalence of gestational diabetes:</u> Royal London Hospital – 11% Whipps Cross University Hospital – 2.5% Newham University Hospital – 13% <u>Rate of addition of pharmacological treatment among women with GDM:</u> Royal London hospital- 41% of GDM required treatment Whipps Cross University Hospital – 39% of GDM required treatment Newham University Hospital – 49% of GDM required treatment **Page 12, lines 7-9**: We thank the reviewer for this suggestion. We have edited the manuscript accordingly to include this. See *"Page 12",* the section titled "*Participant follow-up, Follow-up visits and outcome assessment*", "*Line 7-9*"

Reviewer #2	
Thank you for the opportunity to review the article by Amaefule, et al. entitled "Effectiveness and acceptability of metformin in preventing onset of type 2 diabetes after gestational diabetes in postnatal women: a protocol for a randomized, placebo-controlled, double-blind feasibility trial." This is a protocol paper for the OMAhA study, which will evaluate the feasibility of metformin in the immediate postpartum period to prevent type 2 diabetes among women with a history of GDM. This protocol paper is well-written, and this feasibility study addresses an important public health concern. I would like to make the following comments:	Thank you for this positive comment.
1. In the introduction, the authors state that the "Diabetes Prevention Programme demonstrated that the reduction in type 2 diabetes risk persisted 10 years after commencing metformin after women with gestational diabetes (page 5; lines 29-33)." While I agree with this statement, it would be worth mentioning that all the women with a history of GDM enrolled in the DPP had evidence of impaired glucose tolerance. One novel aspect of the proposed study is that it will involve a broader population of women with GDM, and not just those who already have evidence of impaired glucose tolerance.	1) We thank the reviewer for this comment. Indeed, this highlights the strength of the proposed study as it involves a wider population making the results more generalisable.
2. Will the results of the 6-13 week and 1-year oral glucose tolerance test be blinded to patients enrolled in the study and their usual care providers? If the results will be blinded, under what circumstances will they be revealed to patients and providers? If not blinded, how will the authors safeguard against other interventions being undertaken in clinical care that might influence the study outcomes (i.e.	

use of other medications to reduce the risk for type 2 diabetes, tailored lifestyle counseling, etc.?) 3. How will women who test positive for type 2 diabetes at the 6-13-week visit be managed? Although rare, it is possible that some women who required medical therapy for their GDM will be diagnosed with type 2 diabetes in the immediate postpartum period. Typical standards of care would call for these women to be started on metformin, so it would be helpful if the authors provided additional information about their approach to this subset of women. 4. For the sample size calculations (page 13, line 19) the authors state that they expect at least 1000 women diagnosed with GDM annually are eligible for participation. Can they provide additional information on the total number of deliveries at enrolling hospitals, percent of women with GDM, and percent of women with GDM who are treated with metformin or insulin? This would be very helpful to the reader's understanding of the patient population. 5. How will participants be selected for the quantitative interviews?	2) Participants are informed of the results of their 6-13 week and 1 year oral glucose tolerance test. Participants diagnosed with type 2 diabetes will be withdrawn from the trial and transferred to primary care for further treatment. In this event, if women provide consent, their General Practitioner (GP) is notified of their diagnosis. Upon request, the GP is notified of their treatment allocation to inform further treatment decision. We have edited the manuscript accordingly to include this. See *"Page 13",* the section titled "*Withdrawal criteria*", "*Line 5-9*". 3) Participants diagnosed with type 2 diabetes will be withdrawn from the trial and transferred to primary care for further treatment. In this event, if women provide consent, their General Practitioner (GP) is notified of their diagnosis. Upon request, the GP is notified of their treatment allocation to inform further treatment decision. We have edited the manuscript accordingly to include this. See *"Page 13",* the section titled "*Withdrawal criteria*", "*Line 5-9*". 4) Based on a trust wide audit in 2017, see the below; <u>Annual delivery rate:</u> Royal London Hospital – 6500 Whipps Cross University Hospital – 5,500 Newham University Hospital – 7,000 <u>Prevalence of gestational diabetes</u>

	Royal London Hospital – 11% Whipps Cross University Hospital – 2.5% Newham University Hospital – 13%
6. Page 12, line 36-38 states that maternal and infant outcomes will also be collected as outlined in Figure 1. However, figure 1 only states that maternal and baby outcomes will be collected. It would be helpful if the authors provided more specific information about the outcomes that they will be collecting.	<u>Rate of addition of pharmacological treatment among women with GDM:</u> Royal London hospital- 41% of GDM required treatment Whipps Cross University Hospital – 39% of GDM required treatment Newham University Hospital – 49% of GDM required treatment. 5) Purposive sampling will be used to approach women for qualitative interview. The main goal of purposive sampling is to ensure variation in particular characteristics of the population under study that may influence their response towards the intervention (e.g. previous diagnosis of GDM, parity, ethnicity). The manuscript has been edited to make this clear. See *"Page 14"*, *"Line 13-15"* under the section *"Semi-structured interviews"*. 6) Only maternal and baby outcomes will be collected. We have edited the manuscript accordingly to ensure this is clear. See *"Page 13"*, "*Line 3".*

VERSION 2 – REVIEW

REVIEWER	Christina Scifres Indiana University School of Medicine
REVIEW RETURNED	10-Mar-2020

GENERAL COMMENTS	The authors have responded appropriately to the previous critiques, and the updated version of the manuscript is greatly improved.