Comparative Effectiveness Review Disposition of Comments Report

Research Title: *Management of Postpartum Hypertensive Disorders of Pregnancy*

The draft report was available for public comment from November 29, 2022, to January 10, 2023.

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Comments to Draft Report

Draft reports by the Effective Health Care (EHC) Program undergo peer review and public comment. The Program encourages the public to participate in the development of its research projects. The draft report was posted to the EHC Program website or the Agency for Healthcare Research and Quality (AHRQ) website for public comment for a 6-week period. Comments were submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ.

Summary of Peer Reviewer Comments and Author Response

This research review underwent peer review before the draft report was posted for public comment on the EHC website. Peer reviewers' comments and responses were received from three external reviewers, nine Technical Expert Panel (TEP) members, and one Key Informant (KI)/patient representative and are summarized here.

- Reviewers found the review "*reads well and is clear*" and "*very useful for future research*" and "*highlights paucity of data to help guide clinical management*" and "*the questions of interest were deeply explored.*"
- Several reviewers commented on "*use of the word peripartum.*" One review suggested that "*peripartum is redundant when used to describe preeclampsia with severe features*" and suggested the title "***Management of Postpartum Hypertensive Disorders of Pregnancy***." A reviewer noted that "*the three topics being reviewed together, they seem somewhat discordant*." Several reviewers suggested a natural distinction between "*investigating HBPM and pharmacologic postpartum HTN treatment*" and "*management of peripartum preeclampsia (specifically regarding Magnesium Sulfate)."* The Evidence-based Practice Center (EPC) authors support the shorter title of "Management of Postpartum Hypertensive Disorders of Pregnancy" and plan to submit at least two, possibly three, manuscripts that address the related but distinct key questions.
- Several reviewers commented on clinical applicability. One recommended "*May need to reconsider definitions of Low SOE…which is clinically not helpful"* and discussed *"extrapolating potential treatment effects."* Another reviewer proposed *"Our knowledge about htn treatment for non pregnant and postpartum patient should be employed in the absence of definitive studies for this population to address the known postpartum morbidity."* EPC authors believe these issues are very important for the authors of clinical practice guidelines to consider.
- A reviewer commented that "*I appreciated the nuance and detail provided in the 4.1 Contextual question. There was good coverage of structural and social factors as well as inclusion of bias as root causes on disparities. Good discussion of race a variable in these studies.*" Another reviewer commented that the report should "*discuss in a more detailed the issue of racism and social determinants in this research. This is addressed in the discussion but should also be addressed in the introduction in more detail as well as throughout the document*." The EPC authors have added a brief summary of the proportion of Black individuals to those studies that address disparities or implementation by race.
- Several reviewers provided comments related to reporting of specific outcomes, for example, decreased deep tendon reflexes, breastfeeding issues, and time from delivery to contact with infant. EPC authors reviewed study-specific definitions resulting in clarifying edits and added a reported breastfeeding outcome for one study.
- One reviewer identified a study that might have been missed. On review, EPC authors found this study was included. Other studies were suggested for inclusion. The EPC authors reviewed these studies and confirmed that they did not fulfill our a priori eligibility criteria (e.g., included patients with nonsevere preeclampsia or evaluated an antepartum intervention, such as the CHAP study [PMID: 36070722] and studies of antenatal aspirin).

- A reviewer commented on the use of "*prior eclampsia*" and "*Among patients being treated for eclampsia.*" EPC authors made edits to clearly define and distinguish two distinct patient populations: (1) those with eclampsia, that is, those who were allocated to a magnesium sulfate ($MgSO_4$) treatment regimen after they had experienced at least one eclamptic seizure and (2) patients with preeclampsia with severe features who were allocated to a $MgSO_4$ treatment regimen.

Public Comments and Author Response

Commenter	Section	Comment	Response
Association of Black Cardiologists' (ABC) Cardiovascular Disease in Women and Children Committee		The conclusions reached in the analysis are limited due to modest strength of evidence. As such, the data will not be sufficiently useful to inform clinical practice guidelines. With the overuse of the word "may" in the findings and conclusions, which appears necessary because of the low strength of evidence, it undermines confidence in findings. We appreciate the findings inform priorities for additional research.	Our graded conclusions follow AHRQ EPC Program Guidance. We use "may" to indicate "Low SoE" and "probably" to "Moderate SoE". and are intended to be interpreted in the context of the SR only. We do not intend to imply that low strength-of-evidence conclusions are insufficient to inform practice guidelines or clinical practice.
ABC		Black women encounter barriers that limit effective postpartum care, such as transportation and lack of childcare. The use of self-monitored ambulatory blood pressure machines can be an effective intervention to increase patients undergoing blood pressure readings.[4] We appreciate that among the conclusions of the draft review is home blood pressure monitoring may improve disparities in blood pressure ascertainment between Blacks and non-Blacks.	Thank you
ABC	multiple	We are concerned with the generalized statements in the draft review about the use of diuretics for patients with hypertensive disorders of pregnancy. The document should include some level of stratification of specific underlying etiologies and co-morbid conditions. For instance, how would the use of diuretics differ for those with gestational hypertension versus those with chronic hypertension with superimposed preeclampsia or those with chronic hypertension with preeclampsia with severe features (e.g., intravascular depletion.) What considerations should be given to hypertensive patients with peripartum cardiomyopathy? The draft review could be misconstrued to suggest providers should give diuretics to all patients with hypertensive disorders in the postpartum period. Instead, it should be emphasized in the final review document that administration of diuretics should be determined on a case-by-case basis.	Thank you. We have edited Key Points and Results sections to reflect the specific inclusion criteria used in the Lopes Perdigao 2021 RCT, i.e., "preeclampsia (or gestational HTN) with or without severe features". These questions will need to be considered by the authors of future clinical practice guideline(s) informed in part by this review. In section 4.6 Implications for Research includes a recommendation "to identify clinical factors (e.g., heart rate, edema, biomarkers and comorbidities) that predict a favorable response to a particular medication"

Source: https://effectivehealthcare.ahrq.gov/products/hypertensive-disorders-pregnancy/research
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Commenter	Section	Comment	Response
ABC	Discussion (Section 4.6 Implications for Research)	With regard to shorter regimens of magnesium sulfate, while more research may be warranted, we believe the ethics of stratifying patients to 24 hours versus less time on magnesium may preclude such a study, as the risk of an adverse event (i.e. seizure activity) is high.	In section 3.3.4.1, we estimate a seizure risk of 9 per 1000 patients with preeclampsia with severe features treated with 24-hour $MgSO_4$ regimens in effectiveness trials. Figure 3.2 illustrates a meta-analysis of findings in comparative effectiveness trials, i.e., studies that compared shorter-duration regimens with 24-hour duration regimens. The point estimate for the comparative odds of seizure is 0.72 (lower odds with shorter-duration regimens). However, this estimate is imprecise (hence insufficient for a graded conclusion) and the confidence interval is compatible with an increased odds of seizure. We discuss a "pessimistic" scenario, using the upper 97.5% bound of the confidence interval for the comparative odds of seizure. In this scenario,92 patients would need to receive standard duration therapy to prevent one additional seizure. We agree careful consideration should be given to the ethics and design of clinical trials. We hope our evidence synthesis will assist trialists, funders, IRBs, and informed patients.
ABC		The contextual look at the impact of race/ethnicity and social determinants of health was an important addition to the review, and the review does a good job of outlining issues and implications. However, few studies have addressed differential outcomes between racial/ethnic groups in incidence, detection, treatment, and outcomes of patients with hypertensive disorders of pregnancy. The final review should delineate in the section "Implications for Research" ways to organize future studies to address the contextual question and to determine real solutions to mitigate disparities.	Thank you. We have edited Section 4.6, Implications for Research to begin with a paragraph discussing implications for Research.

Commenter	Section	Comment	Response
ABC		This draft evidence review demonstrates the body of evidence on the management of postpartum hypertensive disorders of pregnancy is grossly inadequate and that future coherent, coordinated inquiry is urgently needed for clear clinical guidance. Citations provided: Bond RM, Gaither K, Nasser SA, et al. Working Agenda for Black Mothers: A Position Paper From the Association of Black Cardiologists on Solutions to Improving Black Maternal Health. Circ Cardiovasc Qual Outcomes. 2021;14(2):e007643. doi:10.1161/CIRCOUTCOMES.120.007643 Kuehn BM. Hypertensive Disorders in Pregnancy Are on the Rise. JAMA. 2022;327(24):2387. doi:10.1001/jama.2022.9510	We agree that future research is needed. Thank you for the references. We have cited the primary source (Ford 2022) reviewed in Keuhn 2022 in the Background section, noting that HDP prevalence is also higher in non-Hispanic American Indian and Alaska Native individuals. Ford ND, Cox S, Ko JY, et al. Hypertensive Disorders in Pregnancy and Mortality at Delivery Hospitalization - United States, 2017-2019. MMWR Morb Mortal Wkly Rep. 2022;71(17):585-591. doi:10.15585/mmwr.mm7117a1
The National Center for Health Research (NCHR)	Background	The abysmal maternal mortality rate and its striking racial disparities in the U.S. must be addressed. Approximately 53% of maternal deaths occur postpartum – between one week and one year after delivery.1 Of these, about 6.5% are caused by hypertensive disorders of pregnancy. Data on 1,018 pregnancy-related deaths among residents of 36 states from 2017 to 2019 found that 84% of these deaths were preventable.	Thank you for updated data for the 2017 to 2019 period. We have cited the source for these data (below) and updated percentages of deaths attributable to HDP in Black individuals (9.9%) versus 4.8 % in White-nonHispanic individuals. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017–2019
NCHR	General	We applaud the AHRQ for completing this comprehensive review to help healthcare providers and policymakers develop clinical practice guidelines that are designed to enhance care for women during this critical period. This review highlights the importance of the postpartum period in the health of women and children. According to the American College of Obstetricians and Gynecologists (ACOG), postpartum care should be considered an ongoing process rather than an isolated visit. We agree with ACOG that “the lack of policies substantially benefitting early life in the United States constitutes a grave social injustice: those already most disadvantaged in our society bear the greatest burden.”2	We thank NCHR for reviewing and providing comments.

Commenter	Section	Comment	Response
NCHR	General	The review focuses on practical issues regarding the effectiveness of home blood pressure monitoring and diuretics, as well as the best regimens for magnesium sulfate use for pre-eclampsia. The agency points out the need for additional quality research into the comparative benefits and harms of both commonly-used and alternative antihypertensives, the impact of home blood pressure monitoring on clinical outcomes, and the best use of magnesium sulfate to reduce side effects and toxicity. The comparative review found mixed outcomes across studies, many studies with a short duration of follow-up, and too few studies to draw conclusions about long-term effects.	We thank NCHR for the succinct summary of our review.
NCHR	General	We are encouraged by the agency's conclusion that home blood pressure monitoring may be beneficial. During the COVID-19 pandemic, many healthcare providers turned to at-home patient monitoring tools to keep track of vital patient information without requiring in-person office visits. AHRQ found that home blood pressure monitoring not only improves the likelihood that patients will check their blood pressure but also helps reduce racial disparities in adherence to recommended blood pressure surveillance. For example, one randomized controlled trial of a text-message-based blood pressure surveillance program found that the blood pressure measurement and reporting rate was over 90% for Black and non-Black women – representing a 50% absolute reduction in racial disparity. Of the 103 women in each arm of the trial, no women in the treatment arm required hospital readmission, compared to four women in the control arm. Therefore, we urge policymakers to use these findings to make home blood pressure monitoring accessible to a wider range of patients. This may mean requiring insurers to extend postpartum medical coverage for a longer period of time and ensuring that medical devices are covered for postpartum women.	Thank you.

Commenter	Section	Comment	Response
Seuli Brill Physician, Health Services Research, Ohio State University College of Medicine		Regarding: "Diuretics may shorten the duration of postpartum hypertension by more than half (low SoE). There was insufficient evidence regarding the comparative benefits and harms of other antihypertensive medications." There is some literature that discusses the potential of diuretics to suppress lactation. Even if definitive evidence isn't available,since widely accessed clinical literature/ resources (such as the LactMed database) provide this guidance, it may be beneficial to more specifically call out comparative benefits/ harms specific to lactation (both across diuretic classes e.g. loop/ thiazide) and more broadly across classes. 1) https://www.ncbi.nlm.nih.gov/books/NBK500965/ 2) https://www.ncbi.nlm.nih.gov/books/NBK500810/ 3) https://onlinelibrary.wiley.com/doi/full/10.1111/j.1527-3466.2007.00036.x#b3 4) https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/aogs.14378	Thank you for the citations. We have edited the background to note that "postpartum HDP may impact breastfeeding practice and experience" and have referenced citation #4, Horsley 2022 (PMID 35610941) Our eligibility criteria did not include all study types, or secondary sources of evidence, e.g. LactMed. Narrative reviews, such as citation #3 were excluded. Regarding citation #1 (LactMed), we found no studies with a hydrochlorothiazide (HCTZ) treatment arm that met our inclusion criteria. In Section 4.6 Implications for Research, we include a HCTZ as an example of medications that should be evaluated in comparative trials, and emphasize the need to evaluate the impact on breastfeeding. Citation #2 (LactMed) cites the breastfeeding outcome reported Lopes Perdiago 2021, which is included in our report.

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical		The AHRQ Assessment on the Management of Postpartum Hypertensive Disorders of Pregnancy provides a summary of clinical evidence addressing the management of postpartum Hypertensive disorders of pregnancy (HDP). Identification of patients at risk during pregnancy as well as optimizing management of hypertensive disorders of pregnancy likely impacts the incidence, severity and associated hypertension complications in post-partum women. While the assessment reviews clinical evidence for Home Blood Pressure Monitoring (HBPM), it does not take into account additional digital vascular biomarker measurements of arterial health parameters such as central blood pressure (cBP), central pulse pressure and augmentation index which may provide further insight and guide treatment in this specific patient population. We request the AHRQ consider the clinical evidence supporting these additional parameters in the assessment. Please see the attached document for further detail (appended below) The AHRQ Assessment on the Management of Postpartum Hypertensive Disorders of Pregnancy provides a summary of clinical evidence addressing the management of postpartum Hypertensive disorders of pregnancy (HDP). Identification of patients at risk during pregnancy as well as optimizing management of hypertensive disorders of pregnancy, likely impacts the incidence, severity and associated hypertension complications in post-partum women. While the assessment reviews clinical evidence for Home Blood Pressure Monitoring (HBPM), it does not take into account additional digital vascular biomarker measurements of arterial health parameters such as central blood pressure (cBP), central pulse pressure and augmentation index which may provide further insight and guide treatment in this specific patient population. We request the AHRQ consider the clinical evidence supporting these additional parameters in the assessment.	Thank you for your comments. In our search, we did not find any studies that utilized home blood pressure monitors that incorporated digital vascular biomarker measurements. Thank you for the background with citations. None of the papers cited meet our predefined study inclusion criteria.

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		Background Management of hypertension through cuff measurement of peripheral (brachial artery) pressures, which has been in use since the 1800's, has dramatically but incompletely improved the ability of health care providers and their patients to control hypertension and reduce associated end-organ damage. Multiple issues likely contribute to the ongoing socioeconomic burden of hypertension, including hypertensive disorders of pregnancy, despite the availability of multiple effective medications and widespread educational efforts. Such issues include, but are not limited to, case finding (early diagnosis), continuity and continued follow-up of care, affordability of care, medication adverse effects, medication compliance and challenges in modifying lifestyle behavior. Central Blood Pressure / Aortic Pressures An underappreciated but clinically relevant area to consider is the precision and reliability of current monitoring which is based on brachial blood pressure measurements, including patient and health care provider factors. In general, cuff brachial blood pressure might be viewed as a surrogate for central (i.e., aortic) blood pressures; however, differences exist between brachial and aortic pressures and the differences can vary among different individuals.(Pauca, McEniery 2008, McEniery 2014) Aortic pressure represents the actual pressure that is transmitted to organs effected by hypertension (e.g., heart, brain, kidney) due to the closer proximity of the ascending aorta to these vital organs. Non-invasive pulse wave analysis (PWA) is a technique that transforms the peripheral (brachial) arterial pressure waveforms into central aortic pressures with cardiovascular related features and digital vascular biomarkers for routine monitoring, including the following: • Central aortic systolic and diastolic pressures • Augmentation index (ratio expressing the relationship of forward and backward traveling waves in the central aorta) • Central aortic pulse pressure (systolic minus diastolic pressure).	(response above)

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		• Pulse pressure amplification (the ratio of peripheral to central pulse pressure) Peripheral (brachial) blood pressures are highly correlated to central pressures; however, significant variability exists such that central pressures cannot be reliably inferred from brachial pressures. Additionally, brachial systolic pressures are generally higher than central aortic pressures although diastolic pressures are similar. The ability to obtain and quantify these variables provide an in-depth understanding of vascular physiology and help determine risk and potential treatment strategies. The value of cBP has been demonstrated in multiple landmark studies using the SphygmoCor XCEL device. The Strong Heart Study of 3,500 high-risk adults showed that central pulse pressure was 50% better than brachial pulse pressure in predicting cardiovascular events. (Roman) A study of 1,648 pregnant women found cBP and related parameters to be the best predictor for the later development of hypertension whereas bBP was not predictive. (Marozio) Such finding is consistent with the view that, while related, bBP and cBP are not interchangeable. Central Blood Pressure During Pregnancy and Post-Partum In observational studies of women with hypertensive disorders of pregnancy, worsening of hypertension was noted between days 3–6 postpartum. (Hauspurg) This increase in blood pressure is typically seen after discharge from the hospital and is associated with maternal morbidity and mortality. Furthermore, the traditional 6-week postpartum visit is poorly attended, with studies showing that up to 40% of women are not seen in follow-up after delivery. As the most common etiology of postpartum readmissions, hypertensive disorders of pregnancy come with a significant associated postpartum socioeconomic burden.	(response above)

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		Marozio et al examined the possible correlation between PWA parameters measured during the first trimester of pregnancy in normotensive, low-risk women and the development of hypertensive disorders later in pregnancy.(Marozio) The study population (n=1,648) was recruited at the time of prenatal screening for chromosomal abnormalities (11+0 to 12+6 weeks of gestation). The values of central aortic systolic pressure, central aortic diastolic pressure, central aortic mean pressure, central aortic pulse pressure, and AIx-75 measured in the first trimester of pregnancy were significantly higher in the women who later developed hypertensive disorders of pregnancy than in those who remained normotensive ($p<0.0001$ for all except for aortic pulse pressure ($p=0.014$)). The aortic systolic pressure (sensitivity 72.6%; specificity 59.6%) was found to be the best predictor for the later development of hypertension. Brachial BP was not predictive of the subsequent development of hypertensive disorders of pregnancy, which is consistent with the view that, while correlated, brachial BP and central aortic BP are not interchangeable. The incidence of preterm hypertensive disorders of pregnancy, particularly of preterm, early-onset preeclampsia, was too low to allow subgroup analysis of the predictive performance of PWA parameters. The authors concluded that in normotensive, low-risk pregnant women, PWA may be useful for the early detection of risk for the development of hypertensive disorders of pregnancy and may allow for targeted surveillance and preventive intervention.	(response above)

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		A report in 2012 evaluated the potential value of assessment of central aortic systolic BP (cSBP), pulse wave velocity (PWV) and AIx at 11-13 weeks gestation in identifying women who subsequently develop pre-eclampsia.(Khalil) Maternal history and characteristics were recorded and PWV, AIx-75 and cSBP were measured. Women who developed pre-eclampsia (n=181) were compared to those in unaffected controls (n=6,766). In the pre-eclampsia group, compared to unaffected controls, there was an increase in AIx-75 (p<0.0001), PWV (p<0.0001) and cSBP (p<0.0001). cSBP had the highest predictive value for preeclampsia. It was particularly notable that in the group with chronic hypertension, in those who developed PE, compared to those who did not, the cSBP (1.29 vs.1.15 multiples of the median of the control group (MoM); p=0.001) was increased but there was no significant difference in PWV (1.02 vs.1.00 MoM; p=0.921) or AIx-75 (1.37 vs. 1.21 MoM; p=0.104). The authors concluded that compared with women who remain normotensive, women who develop pre-eclampsia have higher cSBP and arterial stiffness (as measured by PWV and AIx-75), which is apparent from the first trimester of pregnancy. A report by Anvi et al sought to examine whether PWA could discriminate between normal and hypertensive pregnancies. (Anvi) One hundred pregnant women were studied: five with severe pre-eclampsia, 27 with gestational hypertension, 14 with chronic hypertension and 54 with normal pregnancy. Augmentation pressure, AIx and AIx-75 were significantly higher in women with gestational hypertension and pre-eclampsia compared with normal pregnancies and women with chronic hypertension (p < 0.05 for all). There were no significant differences between normal pregnancies and women with chronic hypertension (p > 0.05 for all comparisons). AIx and augmentation pressure were significantly different among groups even after adjusting for peripheral BP. The study provides further support to the utility of adding measurement of central aortic pressures to standard brachial blood pressure measurements.	(response above)

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		Hausvater and colleagues conducted a systematic review and meta-analysis to investigate the association between preeclampsia and arterial stiffness as measured by PWA and pulse wave velocity (PWV).(Hauvaster) Twenty-three relevant studies were included. A significant increase in all arterial stiffness indices combined was observed in women with preeclampsia compared to women with normotensive pregnancies [standardized mean difference 1.62, 95% confidence interval (CI) 0.73-2.50]. Carotid-femoral pulse wave velocity and augmentation index (AIx) were significantly increased, whereas carotid-radial PWV increase did not reach significance. Significant increases in arterial stiffness measurements were noted in women with preeclampsia compared with those with gestational hypertension. The data indicate that arterial stiffness measurements may be useful in predicting preeclampsia and may play a role in the increased risk of future cardiovascular complications seen in women with a history of preeclampsia. Recognizing the underutilization of postpartum care and the increasing morbidity in this period, the ACOG has suggested the use of telemedicine or remote healthcare interventions to facilitate postpartum care. We strongly support this position and advocate for the inclusion of digital vascular biomarker measurements as additional arterial health parameters, including cBP, which we believe will provide a significant part of the missing puzzle pieces in improving maternal health outcomes. References Avni B., Frenkel G., Shahar L., Golik A., Sherman D., Dishy V. Aortic stiffness in normal and hypertensive pregnancy. Blood Pressure 2010;19:11-15. Hauspurg A, Parry S, Mercer BM, Grobman W, Hatfield T, Silver RM, Parker CB, Haas DM, Iams JD, Saade GR, Wapner RJ, Reddy UM, Simhan H. Blood pressure trajectory and category and risk of hypertensive disorders of pregnancy in nulliparous women. Am J Obstet Gynecol. 2019 Sep;221(3):277.e1-277.e8. doi: 10.1016/j.ajog.2019.06.031. Epub 2019 Jun 27. PMID: 31255629; PMCID: PMC6732036.	(response above)

Commenter	Section	Comment	Response
Rhonda Welch VP Market Access Atcor Medical (cont'd)		Hausvater A, Giannnone T, Gomez Sandoval YH, Doonan RJ, Antonopoulos CN, Matsoukas IL, Petridou ET, Daskalopoulou SS. The association between preeclampsia and arterial stiffness. J Hypertension 2012;31:17-33. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics in normal pregnancies at 11-13 weeks' gestation. Fetal Diagn Ther 2012; 32:179–185. Marozio L, Chiarle G, Filippini C, Challancin S, Tancredi A, Viora E, Benedetto C. Arterial stiffness in normal pregnancy at11 13 weeks of gestation and risk of late-onset hypertensive disorders of pregnancy. J Hypertension 2019;37:1018-22. McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace S, Rowe C, Cockcroft JR, Wilkinson IB, on Behalf of the Anglo-Cardiff Collaborative Trial Investigators. Central pressure: variability and impact of cardiovascular risk factors. The Anglo-Cardiff Collaborative Trial II. Hypertension. 2008;51:1476-1482. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. European Heart Journal (2014) 35, 1719–1725 Pauca A, O'Rourke MF, Kon N. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension. 2001;38:932-937 Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension. 2007 Jul;50(1):197-203. doi: 10.1161/HYPERTENSIONAHA.107.089078. Epub 2007 May 7. PMID: 17485598.	(response above)

Commenter	Section	Comment	Response
Ann Celi BWH Division of General Medicine and Primary Care BWH/Harvard Medical School Physician clinical innovator, educator, investigator	Background ES-2, pg 2	In the background and purpose section page ES-2 paragraph 2 the new version does not mention or emphasize the importance of medication dose intervals that favor adherence.	Background edited to include dosing intervals that favor adherence (for brevity, we've retained "which medication(s) are most effective" in the ES. In Section 4.6 Implications for Research, we have edited to recommend that trial design and analysis should evaluate if comparative effectiveness may be in part mediated by improved adherence to a medication, e.g., XR nifedipine, with a longer dosing interval.
Ann Celi	Future research	There is emphasis on the disparities of black vs. white, Hispanic vs. non-Hispanic however, there needs to be mention of the poor health outcomes in indigenous native communities and disparities in care. please mention with health care innovations the importance of addressing the digital and health care literacy divide	In 4.6 Implications for Research, we have edited to elaborate on the need for research to address the particular needs of vulnerable individuals in diverse communities.
Ann Celi		in first paragraph there is an acknowledgement of health care outcomes disparities in indigenous communities! This needs to be amplified and explained in further detail, call out paucity of work compared to black populations disparities. call out the heterogeneity of vulnerable populations and groups and the multimodal approaches to be employed to address issues. Also lacks discussion of urban/rural issues, promote and encourage advent of telehealth for rural outreach. Please emphasize again optimizing and minimizing daily doses to promote adherence	We have edited Background and Section 4.6, Implications for Research, to highlight "the particular needs of vulnerable individuals in diverse communities (e.g., Native Americans, and Alaska Native), settings (e.g., rural communities)" In Section 4.3, Applicability, we highlight potential benefit and challenges in the rural setting. See (row 13) above.

Commenter	Section	Comment	Response
Ann Celi		Question 9 I was on the technical expert panel and was also a key informant. My more extensive review comments were already shared, points I felt were either edited out of still requiring emphasis are noted on this form Question 10 yes. excellent work Question 11 yes, clear and easy to understand. a more complicated discussion of race/ethnicity (to include native populations) I think would be beneficial	Thank you for your contributions. Thank you. See above.