HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Am J Obstet Gynecol. 2017 September ; 217(3): 249–262. doi:10.1016/j.ajog.2017.05.058.

Research standardization tools: Pregnancy measures in the PhenX Toolkit

Ann Kinga Malinowski, MD, MSc[1], **Cande V. Ananth, PhD, MPH**[2], **Patrick Catalano, MD**[3], **Erin P. Hines, PhD**[4], **Russell S. Kirby, PhD**[5], **Mark A. Klebanoff, MD**[6], **John J. Mulvihill, MD**[7], **Hyagriv Simhan, MD, MS**[8], **Carol M. Hamilton, PhD**[9], **Ms. Tabitha P. Hendershot, BA**[9], **Mr. Michael J. Phillips, MS**[9], **Ms. Lisa A. Kilpatrick, MS**[9], **Ms. Deborah R. Maiese, MPA**[9], **Erin M. Ramos, PhD**[7], **Rosalind J. Wright, MD**[10], and **Siobhan M. Dolan, MD, MPH**[11] **for the PhenX Pregnancy Working Group**

[1]Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Mt. Sinai Hospital, Lunenfeld-Tanenbaum Research Institute, University of Toronto, ON, Canada

[2]Department of Obstetrics and Gynecology, College of Physicians and Surgeons, and Department of Epidemiology, Joseph L. Mailman School of Public Health, New York, NY, United States

[3]Case Western Reserve University, Cleveland, OH, United States

[4]U.S. Environmental Protection Agency, Research Triangle Park, NC, United States

[5]University of South Florida, Tampa, FL, United States

[6]The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States

[7]National Human Genome Research Institute, Bethesda, MD, United States

[8]Department of Obstetrics, Gynecology and Reproductive Science, Division of Maternal-Fetal Medicine, University of Pittsburgh, Pittsburgh, PA, United States

[9]RTI International, Research Triangle Park, NC, United States

[10]Icahn School of Medicine, New York, NY, United States

[11]Albert Einstein College of Medicine, Bronx, NY, United States

Corresponding Author: A. Kinga Malinowski, 700 University Ave., 3rd Floor, Suite 3-909, Toronto, ON M5G 1Z5, Ph (work): 1-416-586-4800 ext. 5309, Ph (cell): 1-647-984-1901, Fax: 1-416-586-8740, amalinowski@mtsinai.on.ca.

Conflict of Interest/Disclosure Statement: The authors report no conflicts of interest.

Disclosures: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the U.S. Environmental Protection Agency and National Institutes of Health.

Disclaimer: This work represents the opinions of the authors and does not represent the official policy of the U.S. Environmental Protection Agency or the National Institutes of Health.

Paper Presentation Information: Presented at the 66th Annual Meeting of the American Society for Human Genetics Vancouver, Canada, October 16–22, 2016; the National Institute of Environmental Health Sciences, NIEHS Environmental Health Sciences Fest, Research Triangle Park, NC, December 5–8, 2016; and 56th Annual Meeting of the Society of Toxicology, Baltimore, MD, March 12–16, 2017.

Abstract

Only through concerted and well-executed research endeavors can we gain the requisite knowledge to advance pregnancy care and positively impact maternal and newborn health. Yet the heterogeneity inherent in individual studies limits our ability to compare and synthesize study results, thus impeding the capacity to draw meaningful conclusions that can be trusted to inform clinical care. The PhenX Toolkit (http://www.phenxtoolkit.org), supported since 2007 by the National Institutes of Health, is a web-based catalog of standardized protocols for measuring phenotypes and exposures relevant for clinical research. In 2016, a working group of pregnancy experts recommended 15 measures for the PhenX Toolkit that are highly relevant to pregnancy research. The working group followed the established PhenX consensus process to recommend protocols that are broadly validated, well-established, nonproprietary, and have a relatively low burden for investigators and participants. The working group considered input from the pregnancy experts and the broader research community and included measures addressing mode of conception, gestational age, fetal growth assessment, prenatal care, mode of delivery, gestational diabetes, behavioral and mental health, and environmental exposure biomarkers. These pregnancy measures complement the existing measures for other established domains in the PhenX Toolkit, including reproductive health, anthropometrics, demographic characteristics, and alcohol, tobacco, and other substances. The preceding domains influence a woman's health during pregnancy. For each measure, the PhenX Toolkit includes data dictionaries and data collection worksheets that facilitate incorporation of the protocol into new or existing studies. The measures within the pregnancy domain offer a valuable resource to investigators and clinicians and are well poised to facilitate collaborative pregnancy research with the goal to improve patient care. To achieve this aim, investigators whose work includes the perinatal population are encouraged to utilize the PhenX Toolkit in the design and implementation of their studies, thus potentially reducing heterogeneity in data measures across studies. Such an effort will enhance the overall impact of individual studies and increasing the ability to draw more meaningful conclusions that can then be translated into clinical practice.

Keywords

Conception; cross-study analyses; data harmonization; delivery; depression; environmental exposure biomarkers; epidemiologic surveys; fetal growth assessment; gestational age; gestational diabetes; mental health; phenotypes; PhenX; PhenX Toolkit; pregnancy; prenatal care; standard measures

Introduction

The principal goals of the practice of medicine are to promote health: forestall disease, offer a cure when feasible, and ease suffering when a cure is not an option.[1] Historically, attempts to reach these goals have included unproven treatments based on traditional mores, convention, or sometimes solely relying on the practitioner's instinct.[2] This changed dramatically with the introduction of the concept of *evidence-based medicine* (EBM), defined as the scrupulous and astute incorporation of the best available evidence into clinical decision-making for individual patients.[3] Clinicians practicing EBM rely on a combination

of their expertise and the best available evidence;[4] for the process to be effective, this evidence must be valid, clear, and consistent.

The first step in achieving this aim is to recognize the existence of heterogeneity inherent in individual studies and the limits that this imposes on between-study comparisons and meta-analysis of data;[5] these limits are further compounded by inexact or absent definitions of measures and outcomes, which are inherent in many reports of original research.[6] Curtailing such barriers at the origin of a study is apt to be the most successful strategy leveraged to enable harmonization of research endeavors. The creation of an easily accessible, common set of measures and outcomes for use by researchers worldwide provides an opportunity to do so.

This is the intention of an effort known as the consensus measures for **Phen**otypes and e**X**posures (PhenX) project,[7] funded as a genomic resource by the National Institutes of Health (NIH) and led by RTI International. PhenX is driven by the scientific community, with overall guidance provided by the PhenX Steering Committee (SC). Measures for the Toolkit are selected using an established consensus process.[8] Launched in 2007, the goal of PhenX is to deliver high-quality, low-burden, well-established measures to facilitate cross-study analysis of genome-wide association studies, where even optimally designed individual investigations often lack sufficient sample sizes to address statistical power stipulations.[9] The original scope of the PhenX project included 20 research domains, with a *domain* defined as an area of investigation with common features and clearly itemized measures.[7] Some of the original domains included demographics, anthropometrics, complex medical conditions (e.g., diabetes, cancer), body systems (e.g., ocular, respiratory), and exposures (e.g., nutrition and dietary supplements, physical activity and physical fitness).[7] For each domain, a Working Group (WG) of from six to nine experts, chosen to balance domain expertise with proficiency in epidemiology, biostatistics, and genomics research, was convened and tasked with selecting (via consensus) 15 measures for inclusion in the PhenX Toolkit.[7] Available at no cost, the PhenX Toolkit (https://www.phenxtoolkit.org) is a web-based catalog that provides ready access to the standard measures of each domain, along with protocols for their use. In 2013, the scope of the PhenX project was expanded to embrace rare genetic conditions and a variety of study designs, as well as four new domains, and the April 2017 version 21.0 of the PhenX Toolkit contains 523 measures in 24 domains;[10] one of these domains is pregnancy.

Pregnancy is a critical time during which exposures have the potential to influence the fetal phenotype significantly, as demonstrated through evolving areas of study, such as the *exposome* (the sum of all environmental exposures from conception through the lifespan),[11] and investigation into the *developmental origins of health and disease* (the hypothesis that in utero exposures at critical times induce certain changes in the fetus, some of which are at the epigenetic level, for instance, in preparation for the ex utero environment).[12] Data collected about lifestyle and biomarkers that represent environmental exposures are essential to fully understand the factors that influence maternal and fetal/neonatal health.[13] Thus, the vital need for utilization of standard measures in studies focused on the perinatal period is readily apparent, and the importance of including pregnancy as one of the PhenX Toolkit domains easily follows, supporting the American Congress of Obstetricians and Gynecologists

(ACOG) endorsement of standardization of practice to improve clinical care and health outcomes.[14]

Recognizing this critical need, the PhenX Pregnancy Working Group (PWG) was prioritized by the PhenX-SC. The aim of this report is to describe the consensus process and results of the PWG's deliberations and to introduce the Pregnancy domain measures included in the PhenX Toolkit.

Material and Methods

The PhenX SC, with input from the NIH PhenX liaisons, established the PWG, identifying individuals on the basis of their expertise, making a deliberate effort to include senior and junior investigators, clinician scientists, academic researchers, and at least one geneticist.[8] The nine PWG members represented obstetrics, maternal-fetal medicine, pediatrics, reproductive genetics, perinatal and reproductive epidemiology, biostatistics, and toxicology. Also involved were personnel from RTI International and a representative from the PhenX-SC. The PWG roster is available on the PhenX website: https://www.phenx.org/Default.aspx?tabid=1066.

The PhenX SC developed the initial scope of the Pregnancy domain, elements of which were refined by the PWG via a review of the PhenX Toolkit to ascertain currently existing measures, thereby allowing for cross-linkage with the new measures and avoiding duplication. Following this review, the PWG selected 15 high-priority measures reflective of the domain, recommending an established and readily available protocol for each measure according to the selection criteria previously developed by the SC (Table 1). Consensus on preliminary measures was reached following deliberations in the form of a 1-day in-person meeting where proposals for measures and protocols were presented by the PWG members for discussion as well as subsequent conference calls, e-mail exchanges, and portal discussions. The PWG then sought input on these preliminary measures from the scientific research community, reviewed data gathered from the outreach, and selected the final measures for inclusion in the PhenX Toolkit (Figure 1). These measures were approved by the SC for release in the PhenX Toolkit. As part of the release, data collection worksheets and dictionaries were created, the measures were linked to “essential” and “related” measures of relevance (terms described below), and keywords were associated with the Smart Query Tool.

An *essential measure* is defined as one that is critical or integral to the collection of the chosen measure; without it, data would be incomplete or interpretation of results compromised.[7] A *related measure* is defined as a suggested, additional PhenX measure, which may be of value to allow a researcher to use the chosen measure to its full capacity. The related measure may, for instance, permit calculation of a derived variable (e.g., height and weight for the calculation of Body Mass Index), or it may be conceptually linked to the chosen measure (e.g., Annual Family Income and Current Educational Attainment).

Results

The Pregnancy domain is unique, yet it is closely related to specific elements already addressed by existing PhenX domains, especially the Reproductive Health domain. To refine the initial scope of the Pregnancy domain, a review of the PhenX Toolkit identified 44 existing measures that are deemed relevant and applicable to research focusing on the perinatal period. These are listed in Table 2, and detailed protocols can be found at https://www.phenxtoolkit.org/index.php?pageLink=browse.relevantmeasures&id=3045.

Following this review, the process of selecting the new measures unfolded over 7 months of deliberations, with an in-person meeting taking place on May 23, 2016, in Bethesda, MD. This meeting culminated in the PWG's recommendation to add 15 new measures to the PhenX Toolkit, reflecting the Pregnancy domain that has yet to be explored by other WGs (Table 3). These were then connected with pertinent essential and related measures (Table 4, providing easy access to measures that relate to one another, thereby allowing researchers to contemplate the inclusion of other measures they may not have otherwise considered.

To highlight the structure of the Toolkit, three of the included Pregnancy measures are characterized in more detail and several other measures that were considered are discussed.

Select PhenX Measures

Gestational Age—Gestational age is an essential component of research on pregnancy outcomes. It is often used for stratification purposes, influences interpretation of many related measures, and is inversely associated with many neonatal complications. Preterm birth closely correlates with many adverse neonatal outcomes and its estimates are higher when best obstetric estimates of gestational age (as outlined below) are used.[15] The PWG recommends that gestational age be established using criteria for determination of estimated due date (EDD) adapted from ACOG,[16] the American Institute of Ultrasound in Medicine,[16] the Society for Maternal-Fetal Medicine,[16] and the Society of Obstetricians and Gynaecologists of Canada.[17] With natural conception, these criteria are based on correlation of menstrual dating and ultrasound parameters, whereas with assisted reproductive technology (ART), an ART-derived EDD is used. If gestational age cannot be established based on medical record abstraction, a maternal interview can be used as an alternative, although this is the less preferred approach. The protocol chosen to address gestational age via maternal interview originates from the well-established Extremely Low Gestational Age Newborns (ELGAN) Project,[18,19] a large-scale, multicenter, epidemiologic study. Finally, the PWG advocated consideration of the following definitions developed by a work group organized by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)[20] for infants born at particular gestational age time frames: early preterm (<34 weeks, 0 days), late preterm (34 weeks, 0 days to 36 weeks, 6 days), early term (37 weeks, 0 days to 38 weeks, 6 days), full term (39 weeks, 0 days to 40 weeks, 6 days), late term (41 weeks, 0 days to 41 weeks, 6 days), and postterm (≥42 weeks, 0 days).

Fetal Growth Assessment—Fetal growth is a gestational age-dependent measure of fetal size in relation to a defined standard growth curve. Fetal growth at both extremes of pathology (small and large for dates) can negatively impact fetal and neonatal outcomes and

has been linked to various comorbidities in later life.[21],[22]For the measure to be accurate, precise determination of gestational age is required. The fetal growth assessment is a three-step process: (i) ascertainment of estimated fetal weight (EFW); (ii) verification of gestational age at which the EFW was recorded; and (iii) determination of the weight's centile by plotting the EFW at the appropriate gestational age on a predefined fetal growth curve. The *National Standards for Fetal Growth* (NSFG), a NICHD-funded multicenter project, is based on a robust methodology that accounts for racial and ethnic differences in fetal growth in US populations. The PhenX work group proposed the NSFG as the preferred protocol.[23]The protocol is accessible and easy to use, and it does not require major equipment or specialized training. A second protocol, the *International Fetal and Newborn Consortium for the 21st Century* (INTERGROWTH-21st) fetal growth standards was also considered,[24] partly because the standards were developed utilizing methods of the World Health Organization Multicenter Growth Reference Study to complete the Fetal Growth and Longitudinal Study. The PWG recommended these standards as Supplemental Information because debate still exists as to whether pooling of data across the eight geographically diverse study sites was the optimal approach and also because the EFW used to calculate the fetal growth percentiles has not yet been tested outside of the original study.[25],[26]

Prenatal and Postpartum Depression—One in eight new mothers suffer major postpartum depression, and a large majority experience the “baby blues”.[27] The Edinburgh Postnatal Depression Scale© (EPDS) was developed to screen for depression and has been validated in pregnancy.[28] The 10-question self-reported instrument screens for depression in the previous 7 days, with a score above 9 identifying candidates who would benefit from a complete clinical assessment.[27] It is one of the most widely used, validated instruments available, has been translated into numerous languages, and has been used with diverse cultural groups, providing an excellent objective screening measure for studies on the topic.[29-32] Feasibility of the use of EPDS as an initial universal screen for depression in the antenatal and postnatal period to identify those who may benefit from further diagnostic evaluation has also been demonstrated.[33]

Other Measures Considered

When the PhenX SC developed the original scope for this domain, very broad coverage of pregnancy-related research was proposed. In its initial deliberation, the PWG determined that some components of the scope were sufficiently covered elsewhere in the Toolkit, such as dietary intake, nutrients and supplements, and medication use. Other components failed to meet selection criteria, such as inflammatory markers associated with preterm birth (absence of a well-established protocol), biobank samples (no phenotype correlation), preeclampsia (available protocols too complicated and long for widespread use in research that may have a different overall focus), and social media (absence of an established protocol).

One further measure, which was deliberated upon for consideration for inclusion, was “placental assessment”. The placenta provides significant insight into environmental exposures over the course of the gestation, and offers indispensable information about pregnancy outcome, as emphasized by the current NIH *Human Placenta Project*.[34-37] While considered an asset to the domain, the placental assessment protocol lacked the prerequisite

that measures in the PhenX Toolkit must be characterized by an actual phenotype and was added to the Supplemental Information section of the Pregnancy domain as an additional resource for users.

Comment

The PhenX PWG was successful in adding 15 new measures uniquely suited to address outcomes pertinent to the state of pregnancy, which complement previously established measures in the PhenX Toolkit. These well-established, low-burden, high-quality measures offer a valuable resource to investigators and clinicians for whom pregnancy is a primary research focus but are perhaps even more indispensable for those who hold expertise in other areas and wish to include pregnancy-related measures in their studies. With this in mind, the PhenX Toolkit provides not only detailed protocols for collecting the data but also all the information necessary to implement the measure properly.

The work of the PWG expands on the earlier efforts of the Reproductive Health WG. The Reproductive Health domain was recently reviewed by an Expert Review Panel (ERP). New measures and updated protocols for this domain were added in version 21.0 of the Toolkit in April 2017. To ensure that the PhenX Toolkit remains scientifically relevant, all domains are systematically reexamined by ERPs on a rotating basis.

Relevant pregnancy-related measures will also be included in two Pregnancy and Birth Collections:[38] (1) the Pregnancy and Birth Health Conditions Collection (http://phenxtoolkitstage.rti.org/index.php?pageLink=browse.conceptualgroups&id=3385&breadcrumbs=3374,3385), and (2) the Pregnancy and Birth Adverse Pregnancy Outcome Risk Factors Collection(http://phenxtoolkitstage.rti.org/index.php?pageLink=browse.conceptualgroups&id=3293&bread crumbs=3293). Collections in the Toolkit do not provide new measures; instead, they offer an alternate path for accessing the measures of interest, characterized by grouping measures linked by a particular theme.

Several other features within the Toolkit also contribute to a convenient user experience. Measures can be browsed by domain, by collection (e.g., risk factors or life stages),[7] or by a specific measure whereby interrelated measures will be highlighted. The search utility supports keyword and full-text searches to locate relevant measures that can be added to “My Toolkit,” which can be individually set up and saved for download. Each measure is complemented by a downloadable data collection worksheet and data dictionary options. Users who register have the added option of saving their work, sharing their Toolkit with their collaborators, and receiving Toolkit updates. Research Electronic Data Capture (REDCap) data dictionary zip files are also now available for all PhenX protocols through the Shared Library website (https://redcap.vanderbilt.edu/consortium/library/search.php), enabling easy inclusion of PhenX measures in clinical and translational research projects that use REDCap.[39]

Beyond delivering an effortless platform for access and use of common outcome measures, the PhenX Toolkit encourages the use of standard protocols across research studies and establishes common data elements. In addition to the advantages of standard measures as

they apply to genome-wide association studies,[7] these benefits also readily extend to biomedical and epidemiologic investigations. Advantages of standard protocols for collecting data include the ability to combine data (i) from prevailing phenotypic and environmental exposure measures, which are historically collected in individual studies using disparate methods; (ii) from studies on diverse populations, allowing for validation of original findings; (iii) from similar studies to increase statistical power, enabling confirmation of weak associations and exploration of rare diseases.[7]

Despite the numerous benefits of the use of standard measures and protocols, the propensity for each researcher to incorporate a set of uniquely defined variables into their study remains,[40] limiting the ability to meta-analyze data across studies. The PhenX Toolkit stands well poised to champion progress in this regard, and there is evidence that PhenX measures are increasingly recognized across the scientific community. PhenX has been recommended by several NIH institutes in 205 Funding Opportunity Announcements as of March 2017.[41] Furthermore, concerted efforts are underway to align PhenX with other standardization platforms. PhenX collaborates with the National Library of Medicine as well as the database of Genotypes and Phenotypes (dbGaP; https://www.ncbi.nlm.nih.gov/gap), and the data elements are posted in the NIH Common Data Elements Repository (https://cde.nlm.nih.gov/home). This approach enables ready identification of investigations using common variables, which will allow for cross-study analysis.[40]

Expanding on the virtues of data harmonization, Fortier et al. describe two approaches: *stringent*, and *flexible*.[9] The stringent approach calls for collection of data across studies with identical tools and protocols. Its advantages lie in ease of data synthesis, and its disadvantages include (i) the challenge of imposing rigid measures and protocols across studies that are thematically, methodologically, and geographically diverse, and have variable resources and funding; and (ii) restriction of data synthesis solely to studies using the prescribed measures, potentially limiting generalizability and risking bias. Conversely, the flexible approach calls for collection of data across studies with distinct tools and protocols. Its advantages include the capacity for synthesis of existing data and the ability to synthesize data across a wide breadth of studies. Its disadvantages include the challenge of safeguarding sufficient compatibility across studies to allow for valid comparisons, and the challenge of synthesis across a sufficiently large number of investigations to allow for valid conclusions.

Reminiscent of the stringent approach, the PhenX Toolkit utilizes standardized protocols to ensure collected data are directly comparable, which facilitates cross-study analysis.[7] At the same time, PhenX reflects a *flexible* approach by providing investigators with protocols for specific measures particular to different areas of interest (e.g., demographics, physical activity and physical fitness), different patient populations (e.g., age, gender), and different modes of administration (e.g., interview, medical record abstraction, bioassay) to be used, as needed, in addressing specific research questions in a uniform, easily replicable manner.[42] The PhenX Toolkit also supports flexibility by providing custom data dictionaries that are compatible with REDCap and dbGaP.[39],[40]

Another data harmonization effort, the Core Outcome Measures in Effectiveness Trials (COMET) Initiative is an example of the flexible approach. The COMET Initiative catalogs Core Outcome Sets (COS) that were developed using prescribed methodology and pertaining to trials investigating specific clinical conditions.[43-46] It has been endorsed by the CoRe Outcomes in WomeN's health (CROWN) Initiative, which includes editors from more than 50 journals pertaining to women's health,[43] and is encouraged by funding bodies in the United Kingdom,[44] where it originated. COS represents a standardized set of outcomes for a particular health condition, forming the minimum expectation for trial reporting,[44] with additional outcome measures of relevance to the specific study hypothesis to be included at the investigator's discretion.

The stringent and flexible approaches are both valuable in striving for harmonization,[9] and thus the PhenX Toolkit and the COMET Initiative should be viewed as highly complementary entities, with investigators drawing on the strengths of each to achieve the goal of standardization so as to strengthen global research initiatives, with the ultimate goal of improving patient care.

The key strengths of the PhenX Toolkit measures, in general, and of the measures in the Pregnancy domain, in particular, lie in that they are well-established, easily and freely accessible, and chosen with the intent of minimizing the burden on study participants and personnel.[7] The next challenge is to promote these measures' use among investigators worldwide so that the measures are adopted by a critical mass of investigators and that the aim of data synthesis across multiple studies can be realized.[9]

Some of the limitations encountered by the PWG were in part imposed by the stipulations of PhenX, which in fact make the Toolkit robust. Specifically, selecting only 15 high-priority measures and also selecting only protocols meeting criteria for easy accessibility, free availability, and a low-burden nature precluded consideration of certain protocols (e.g. for a multigeneration family history of reproductive issues). Similarly, certain measures had to be abandoned because no suitable protocol could be identified (e.g. pre-eclampsia), decreasing the comprehensiveness of the Pregnancy domain.

Collaborative efforts aimed at standardizing data collection methodologies will improve the quality and consistency of study data. This improvement has the potential to accelerate research progress by allowing data synthesis across studies, contributing to enhanced statistical power and the ability to draw more meaningful conclusions. The creation of the Pregnancy domain with its 15 new measures is well poised to facilitate collaborative pregnancy research. To achieve this aim, investigators whose work includes the perinatal population are encouraged to utilize the PhenX Toolkit in the design and implementation of their studies. Only through concerted and well-executed research endeavors can we gain the requisite knowledge to advance pregnancy care and positively impact maternal and newborn health.

Acknowledgments

Role of Funding Source: RTI International's work on PhenX is funded by the National Human Genome Research Institute (cooperative agreement number U41 HG007050) with co-funding from the National Institute on Drug Abuse.

The authors would like to acknowledge the contributions of the PhenX liaisons from the National Institutes of Health.

References

1. Callahan D. Managed care and the goals of medicine. J Am Geriatr Soc. 1998; 46:385–8. [PubMed: 9514393]
2. Whitley R, Rousseau C, Carpenter-Song E, Kirmayer LJ. Evidence-based medicine: opportunities and challenges in a diverse society. Can J Psychiatry. 2011; 56:514–22. [PubMed: 21959026]
3. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996; 312:71–2. [PubMed: 8555924]
4. Sackett DL. Evidence-based medicine. Seminars in Perinatology. 1997; 21:3–5. [PubMed: 9190027]
5. Chess LE, Gagnier JJ. Applicable or non-applicable: investigations of clinical heterogeneity in systematic reviews. BMC Med Res Methodol. 2016; 16:19. [PubMed: 26883215]
6. Clarke M. Standardising outcomes for clinical trials and systematic reviews. Trials. 2007; 8:39. [PubMed: 18039365]
7. Hamilton CM, Strader LC, Pratt JG, et al. The PhenX Toolkit: get the most from your measures. Am J Epidemiol. 2011; 174:253–60. [PubMed: 21749974]
8. Maiese, DR., Hendershot, T., Strader, L., et al. RTI Methods Report series. Research Triangle Park, NC: RTI Press publication; 2013. PhenX - establishing a consensus process to select common measures for collaborative research.
9. Fortier I, Doiron D, Burton P, Raina P. Invited commentary: consolidating data harmonization--how to obtain quality and applicability? Am J Epidemiol. 2011; 174:261–4. author reply 65-6. [PubMed: 21749975]
10. PhenX toolkit. Version 21.0. Released April 11, 2017. Available at: http://www.phenxtoolkit.org/
11. Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005; 14:1847–50. [PubMed: 16103423]
12. Swanson JM, Entringer S, Buss C, Wadhwa PD. Developmental origins of health and disease: environmental exposures. Semin Reprod Med. 2009; 27:391–402. [PubMed: 19711249]
13. Buck Louis GM, Sundaram R. Exposome: time for transformative research. Stat Med. 2012; 31:2569–75. [PubMed: 22969025]
14. ACOG Committee on Patient Safety and Quality Improvement. ACOG Committee Opinion No. 526: Standardization of practice to improve outcomes. Obstet Gynecol. 2012; 119:1081–2. [PubMed: 22525933]
15. Duryea EL, McIntire DD, Leveno KJ. The rate of preterm birth in the United States is affected by the method of gestational age assignment. Am J Obstet Gynecol. 2015; 213:231 e1–5. [PubMed: 25935778]
16. American College of Obsetricians and Gynecologists, American Institute of Ultrasound in Medicine, Society for Maternal-Fetal Medicine. Committee opinion no 611: method for estimating due date. Obstet Gynecol. 2014; 124:863–6. [PubMed: 25244460]
17. Butt K, Lim K, Society of O, Gynaecologists of C. Determination of gestational age by ultrasound. J Obstet Gynaecol Can. 2014; 36:171–83. [PubMed: 24518917]
18. O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Hum Dev. 2009; 85:719–25. [PubMed: 19765918]
19. Joseph RM, Korzeniewski SJ, Allred EN, et al. Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a largecohort study

of 10-year-old children born at 23-27 weeks' gestation. Am J Obstet Gynecol. 2017; 216:304 e1–04 e16. [PubMed: 27847193]

20. Spong CY. Defining “term” pregnancy: recommendations from the Defining “Term” Pregnancy Workgroup. JAMA. 2013; 309:2445–6. [PubMed: 23645117]
21. Chiavaroli V, Marcovecchio ML, de Giorgis T, Diesse L, Chiarelli F, Mohn A. Progression of cardio-metabolic risk factors in subjects born small and large for gestational age. PLoS One. 2014; 9:e104278. [PubMed: 25117750]
22. Wennerstrom EC, Simonsen J, Melbye M. Long-Term Survival of Individuals Born Small and Large for Gestational Age. PLoS One. 2015; 10:e0138594. [PubMed: 26390219]
23. Buck Louis GM, Grewal J, Albert PS, et al. Racial/ethnic standards for fetal growth: the NICHD Fetal Growth Studies. Am J Obstet Gynecol. 2015; 213:449 e1–49 e41. [PubMed: 26410205]
24. Stirnemann J, Villar J, Salomon LJ, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2017; 49:478–86. [PubMed: 27804212]
25. Hanson M, Kiserud T, Visser GH, Brocklehurst P, Schneider EB. Optimal fetal growth: a misconception? Am J Obstet Gynecol. 2015; 213:332 e1–4. [PubMed: 26079625]
26. Villar J, Papageorghiou AT, Pang R, et al. Monitoring human growth and development: a continuum from the womb to the classroom. Am J Obstet Gynecol. 2015; 213:494–9. [PubMed: 26184778]
27. Wisner KL, Parry BL, Piontek CM. Clinical practice. Postpartum depression. N Engl J Med. 2002; 347:194–9. [PubMed: 12124409]
28. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987; 150:782–6. [PubMed: 3651732]
29. Husain N, Rahman A, Husain M, et al. Detecting depression in pregnancy: validation of EPDS in British Pakistani mothers. J Immigr Minor Health. 2014; 16:1085–92. [PubMed: 24469591]
30. Eberhard-Gran M, Eskild A, Tambs K, Opjordsmoen S, Samuelsen SO. Review of validation studies of the Edinburgh Postnatal Depression Scale. Acta Psychiatr Scand. 2001; 104:243–9. [PubMed: 11722298]
31. Adouard F, Glangeaud-Freudenthal NM, Golse B. Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. Arch Womens Ment Health. 2005; 8:89–95. [PubMed: 15883653]
32. Adewuya AO, Ola BA, Dada AO, Fasoto OO. Validation of the Edinburgh Postnatal Depression Scale as a screening tool for depression in late pregnancy among Nigerian women. J Psychosom Obstet Gynaecol. 2006; 27:267–72. [PubMed: 17225628]
33. Venkatesh KK, Nadel H, Blewett D, Freeman MP, Kaimal AJ, Riley LE. Implementation of universal screening for depression during pregnancy: feasibility and impact on obstetric care. Am J Obstet Gynecol. 2016; 215:517 e1–8. [PubMed: 27210067]
34. Sadovsky Y, Clifton VL, Burton GJ. Invigorating placental research through the “Human Placenta Project”. Placenta. 2014; 35:527. [PubMed: 24997635]
35. Guttmacher AE, Spong CY. The human placenta project: it's time for real time. Am J Obstet Gynecol. 2015; 213:S3–5. [PubMed: 26428502]
36. Nelson DM. How the placenta affects your life, from womb to tomb. Am J Obstet Gynecol. 2015; 213:S12–3. [PubMed: 26428490]
37. Thornburg KL, Marshall N. The placenta is the center of the chronic disease universe. Am J Obstet Gynecol. 2015; 213:S14–20. [PubMed: 26428494]
38. Whitehead NS, Hammond JA, Williams MA, et al. The PhenX Toolkit pregnancy and birth collections. Ann Epidemiol. 2012; 22:753–8. [PubMed: 22954959]
39. Phillips M, Grant T, Giampietro P, et al. PhenX measures for phenotyping rare genetic conditions. Genet Med. 2017
40. Pan H, Tryka KA, Vreeman DJ, et al. Using PhenX measures to identify opportunities for cross-study analysis. Hum Mutat. 2012; 33:849–57. [PubMed: 22415805]
41. PhenX Toolkit Funding Opportunity Annoucements (FOAs) - 205. Updated March 16, 2017. Available at: https://www.phenxtoolkit.org/index.php?pageLink=news.funding

42. Hendershot T, Pan H, Haines J, et al. Using the PhenX Toolkit to Add Standard Measures to a Study. Curr Protoc Hum Genet. 2015; 86:1 21 1–17. [PubMed: 26132000]

43. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. BJOG. 2014; 121:1181–2. [PubMed: 24889142]

44. Clarke M, Williamson P. Core outcome sets and trial registries. Trials. 2015; 16:216. [PubMed: 25971905]

45. 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; 211:575–6. [PubMed: 25459559]

46. Khan KS. The CROWN initiative: journal editors invite researchers to develop core outcomes in women's health. Paediatr Perinat Epidemiol. 2014; 28:356–8. [PubMed: 25146721]

47. Haas DM, Parker CB, Wing DA, et al. A description of the methods of the Nulliparous Pregnancy Outcomes Study: monitoring mothers-to-be (nuMoM2b). Am J Obstet Gynecol. 2015; 212:539 e1–39 e24. [PubMed: 25648779]

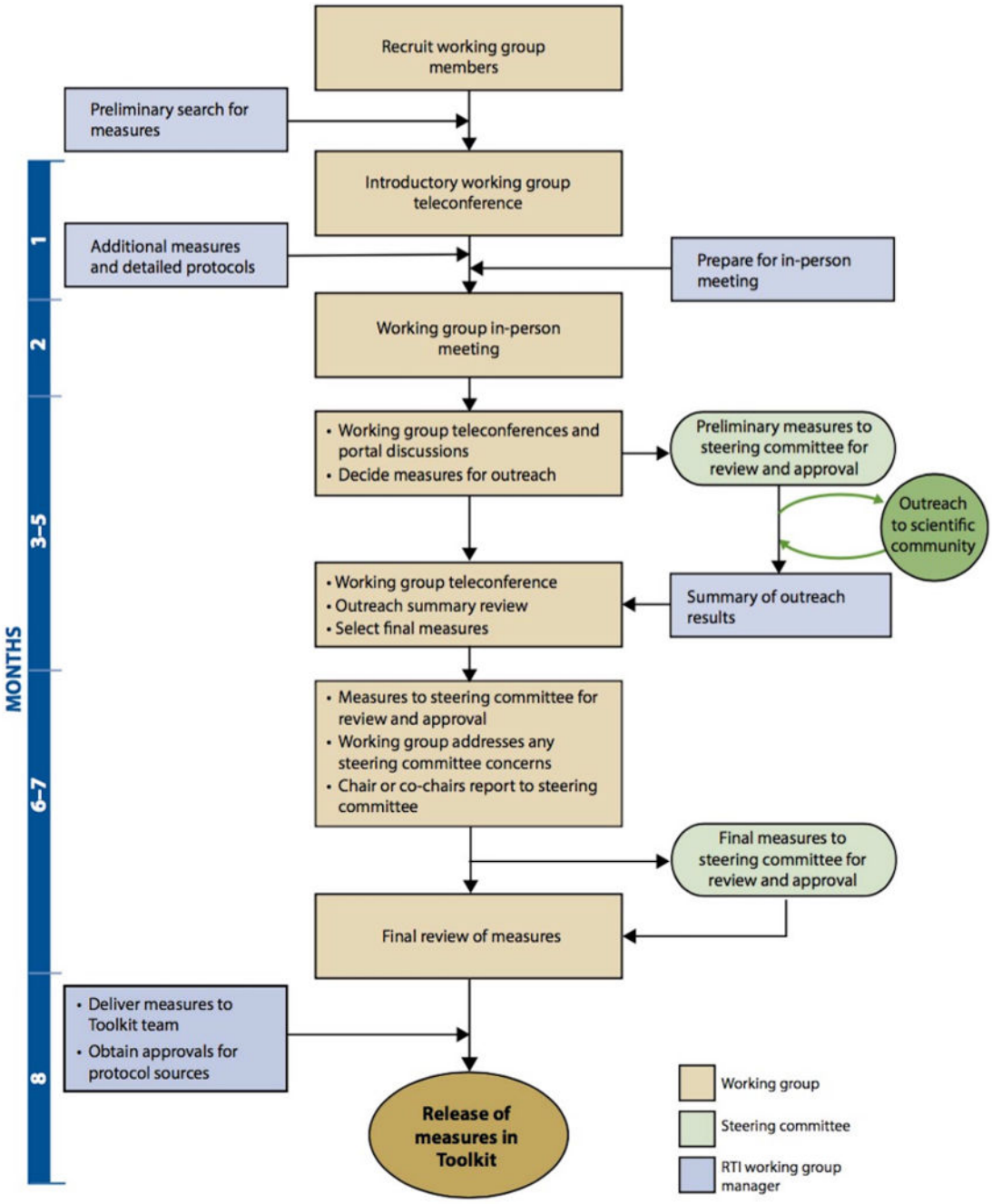

Figure 1. Standard approach to the PhenX consensus process

Originally published by Maiese et al.[8] PhenX—establishing a consensus process to select common measures for collaborative research. 2013. RTI Press and Dr. Maiese have granted permission to the authors to publish this figure.

Table 1

PhenX Toolkit measure criteria

Standard criteria		Additional criteria	
1	Clearly defined	**1**	Crosscutting relevance for population groups as well as diseases and conditions
2	Well-established	**2**	Used in a major reference study (e.g., National Health and Nutrition Examination Survey)
3	Broadly applicable and generally accepted	**3**	Open-source, nonproprietary instrument and software
4	Low burden	**4**	Brevity
5	Utility demonstrated	**5**	Expectation of acceptance by the research community
6	Reproducible		
7	Specific		
8	Reliable		
9	Standard measurement protocols available		

Table 2

Additional relevant measures existing in the PhenX Toolkit and applicable to the pregnancy domain

Existing measure		Domain
Birthplace	Subject	Demographics
	Parents	
	Grandparents	
Cigarette Smoking	Age of first use	Alcohol, Tobacco and Other Substances
	Age of cessation	
	Smoking status	
	Dependence on cigarettes/nicotine	
	Pregnancy status and tobacco use	Tobacco Regulatory Research
	Environmental tobacco smoke exposure	Environmental Exposures
Tobacco[non-cigarette]	Product type	Oral Health
	Use	Tobacco Regulatory Research: Vector
	30-day quantity and frequency	Alcohol, Tobacco and Other Substances
Alcohol	Age of first use	Alcohol, Tobacco and Other Substances
	30-day quantity and frequency	
	Maximum drinks in 24 hours	
	Lifetime use	
	Lifetime abuse and dependence	
Substances	Age of first use	Alcohol, Tobacco and Other Substances
	30-day frequency	
	Lifetime use	
	Lifetime abuse and dependence	
	Patterns of use	Substance Abuse and Addiction
	Screening and severity of substance use problems	Assessment of Substance Use and Substance Use Disorders
Reproductive Health	Ovulation history	Cancer
	History of pre-pubertal development	Reproductive Health
	Assessment of pubertal development	
	Human papilloma virus vaccine use	
	Contraceptive methods	
	Sexual history	
	Menstrual history	
	Reproductive history	
	Female reproductive organ surgical procedures	
	Testes development	
	Male sexual function	
	Prostate health	
	Difficulty conceiving	

Existing measure		Domain
	Causes and treatments of known infertility	
	Hormonal therapy	
	Male reproductive tract birth defects,	
Pregnancy	Pregnancy weight gain	Anthropometrics
	Serial pregnancy weight gain	
	Mother and baby health	Tobacco Regulatory Research
	High blood pressure during pregnancy	Cardiovascular
Medical History	Personal history of type I and type II Diabetes	Diabetes

Table 3
PhenX measures and protocols in the pregnancy domain

Measure name*	Protocol sources	Protocol description and rationale
Adequacy of Prenatal Care	Kotelchuck Index, also called the Adequacy of Prenatal Care Utilization (APNCU)	Adequacy of prenatal care is assessed by the month of the initial visit in the pregnancy and total number of prenatal visits until delivery, with that number being calculated as a percentage of recommended visits. Compared to other utilization of care indexes, the Kotelchuck Index is preferred, as it includes a category for women who receive more than the recommended amount of care (adequate plus, or intensive utilization).
Concentrations of Flame Retardants	NCS, Biospecimen Adult Blood Procedures: Standard Operating Procedures NHANES, CDC Laboratory Procedure Manual, PBDEs	Blood samples are collected and analyzed to determine the concentrations of several PBDEs, which are chemicals used as flame retardants. High concentrations of PBDEs in the blood of a pregnant woman or young child may lead to neurobehavioral problems. The NCS was planned as the largest pregnancy cohort studies in the United States, and the NHANES is a major cross-sectional study in the United States. The collection methods used in both been validated previously.
Concentrations of PCBs and Persistent Pesticides	NCS, Biospecimen Adult Blood Procedures: Standard Operating Procedures NHANES, CDC Laboratory Procedure Manual, PCBs and Persistent Pesticides	Blood samples are collected and analyzed to determine the concentrations of several PCBs and persistent pesticides. Prenatal exposure PCBs may lead to poor cognitive function and attention deficit/ hyperactivity disorder (ADHD). Prenatal exposures to persistent pesticides (e.g., DDT) may have adverse neurodevelopmental effects on children. The NCS was planned as the largest pregnancy cohort studies in the United States, and the NHANES is a major cross-sectional study in the United States. The collection methods used in both been validated previously.
Concentrations of Phenols and Parabens	NCS Biospecimen Adult Urine Procedures: Standard Operating Procedures NHANES Laboratory Procedure Manual, Bisphenol A, Other Environmental Phenols, and Parabens in Urine	Urine samples are collected and analyzed to determine the concentrations of several phenolic compounds such as bisphenol A (BPA) used to make plastic water bottles, baby bottles, and children's toys. This bioassay also permits analysis of parabens, which are chemicals used as preservatives in foods and beverages, cosmetics, and pharmaceuticals. Some phenols and parabens are endocrine disruptors and some have been associated with adverse health effects. The NCS was planned as the largest pregnancy cohort studies in the United States, and the NHANES is a major cross-sectional study in the United States. The collection methods used in both been validated previously.
Concentration of Trace Metals	NCS Biospecimen Adult Blood Procedures: Standard Operating Procedures NHANES, CDC Laboratory Procedure Manual, Cadmium, Lead, Manganese, Mercury, and Selenium	Blood is collected and analyzed to determine the concentrations of trace metals, which may include cadmium, lead, manganese, selenium, and mercury. High concentrations of metals in the blood may cause neurodevelopmental problems, particularly in a developing fetus or in young children. The NCS was planned as one the largest pregnancy cohort studies in the United States, and the NHANES is a major cross-sectional study in the United States. The collection methods used in both been validated previously.
Current Pregnancy Status	(Self-report) NHANES Reproductive Health Module (Assay) NCS, Biospecimen Adult Urine Procedures: Standard Operating Procedures NHANES Mobile Examination Center Laboratory Procedures Manual	This measure is used to determine whether a woman is currently pregnant. It may be needed to determine suitability for participation in a research study and because pregnancy may influence the results of several physical and health measures such as weight and blood pressure. Depending on specific needs and implications, researchers may accept self-report of pregnancy or require a biological sample (urine or blood) for confirmation. The NHANES question on current pregnancy status was chosen for self-report. However, it was acknowledged that a biological assay is the most accurate pregnancy test and should be used for confirmation if pregnancy determination is critical to the study (i.e., prior to certain investigations such computed tomography, or with the use of pharmaceutical agents). The NCS was planned as the largest pregnancy cohort studies in the United States, and the NHANES is a major cross-sectional study in the United States. The collection methods used in both been validated previously.
Difficulties in Pregnancy	nuMoM2b[47] - Difficulties in Pregnancy Visit 1, Form V1E	A measure in the form of a single-item (with 13 subparts) used to capture worries, concerns, and difficulties a woman has experienced related to her pregnancy. Likert-style, self-report questionnaire, administered at 6–13 weeks, and again at 22–29 weeks. The nuMoM2b is a major prospective cohort study collecting data throughout pregnancy on approximately 10,000 nulliparous women. The data collection

Measure name*	Protocol sources	Protocol description and rationale
		instruments were developed by the nuMoM2b investigators in collaboration with Project Scientists from the NICHD.
Family History of Pregnancy Complications	nuMoM2b Difficulties in Pregnancy, Maternal Interview Visit 2	Questions to assess a woman's family history of pregnancy complications. Of relevance, as researchers should be knowledgeable about a woman's family history of pregnancy complications, given some complications may be passed from one generation to the next. The nuMoM2b is a major prospective cohort study collecting data throughout pregnancy on approximately 10,000 nulliparous women. The data collection instruments were developed by the nuMoM2b investigators in collaboration with project scientists from NICHD.
Fetal Growth Assessment	Fetal Growth Standards based on NICHD Fetal Growth Studies	This measure includes abstraction of fetal growth and ultrasound information from a medical record. Fetal growth is a gestational age–dependent measure of fetal size, in relation to a defined standard growth curve. Fetal growth at both extremes of pathology (SGA and LGA) affects fetal and neonatal outcomes, and has been linked with a variety of co-morbidities encountered in later life. The Fetal Growth Standards based on NICHD Fetal Growth Studies offer robust methodology and account for ethnic differences in fetal growth. The protocol is accessible and easy to use. The formula chosen to calculate the EFW, which was then used to develop the fetal growth centiles, is well-known and broadly used. Researchers searching for a protocol for fetal growth assessment can apply this formula with ease to calculate the EFW centile for their study, using ultrasound-derived biometry measures, which are then plotted on the available NICHD growth curves.
Gestational Age (GA)	(Maternal Interview) ELGAN Study Maternal Interview (Medical Record Abstraction) GA	For maternal interview, the protocol originates from the well-established ELGAN Project, a large-scale, multi-center, epidemiologic study. Maternal Record Abstraction is the preferred option for establishing GA, with maternal interview provided as an alternate when medical record abstraction is untenable. GA is established using criteria for determination of EDD adapted from ACOG, AIUM, SMFM, and SOGC. Determination of EDD is based on review and correlation of menstrual dating with ultrasound parameters in natural conception and on ART-derived EDD when ART is used.
Gestational Diabetes	nuMoM2b: CLA Prenatal Labs	Abstraction of prenatal laboratory data to determine the presence of gestational diabetes. Pregnant women are commonly screened for gestational diabetes because untreated or poorly controlled gestational diabetes can cause negative health outcomes for the mother and baby, including macrosomia, hypoglycemia, and increased risk for cesarean section delivery. The nuMoM2b is a major prospective cohort study collecting data throughout pregnancy on approximately 10,000 nulliparous women. The data collection instruments were developed by the nuMoM2b investigators in collaboration with the NICHD.
Health and Wellness in Pregnancy	Early Life Exposure Assessment Tool (ELEAT)	The measure is used to determine a woman's general physical and mental health in the time period surrounding her pregnancy. The ELEAT tool has been used in previous studies.
Mode of Conception	(Maternal Interview) PRAMS Phase 7 Core Questions and Standard Questions (Medical Record Abstraction) ELGAN Chart Abstraction Form	Questions assessing whether medical intervention of any kind was needed to achieve pregnancy. Information about natural or assisted conception (i.e., infertility treatments or reproductive technologies) is essential to determine fertility status. Questions for the maternal interview protocol have been derived from PRAMS, a major ongoing survey. Questions for the medical record abstraction protocol have been derived from the ELGAN project, a large, multicenter epidemiologic study.
Mode of Delivery	(Maternal Interview) PRAMS Phase 7 Standard Questions (Medical Record Abstraction) A Randomized Trial of Induction Versus Expectant Management (ARRIVE)	Information about the initiating event of a woman's delivery, the mode of delivery, and if it was an assisted delivery. The mode of delivery may influence the health of both the mother and the neonate. Questions for the maternal interview protocol have been derived from PRAMS, a major ongoing survey.
Prenatal and Postpartum Depression	Edinburgh Postnatal Depression Scale© (EPDS)	This measure is a questionnaire that can be used to screen for recent symptoms of depression, including perinatal and postnatal depression. There are 10 questions to assess a mother's postnatal depression in the previous 7 days. A depression screening tool helps health care providers assess women for symptoms of depression before and after their pregnancy. The EPDS is

Measure name*	Protocol sources	Protocol description and rationale
		one of the most widely-used, validated self-report instruments to screen for depression during and after pregnancy.
Supplemental information		
Placental Assessment	Amsterdam Placental Workshop Group Consensus Statement & College of American Pathologists Practice Guideline for Examination of the Placenta	A protocol for the histopathologic examination of gross and microscopic placental features. The protocol provides explicit instructions on specimen collection and sampling of placental tissues and guidance on definitions, diagnostic criteria, and classification of placental lesions to assist in international comparability of research studies and continued evolution of knowledge regarding the significance of placental lesions associated with adverse pregnancy and later health outcomes.
International Fetal Growth Standards	Stirnemann J, et al. (2016). International Estimated Fetal Weight Standards of the INTERGROWTH-21st Project. *Ultrasound Obstet Gynecol*. doi: 10.1002/uog.17347 Hadlock FP, et al. (1985). Estimation of fetal weight using head, body and femur measurements - a prospective study. *Am J Obstet Gynecol*, 151:333-337.	This measure includes abstraction of fetal growth and ultrasound information from a medical record.

*All measures and protocols are available at: https://www.phenxtoolkit.org/index.php?pageLink=browse.measures&id=240000 ACOG – American Congress of Obstetricians and Gynecologists; AIUM – American Institute of Ultrasound in Medicine; ART – Assisted Reproductive Technology; BPA – bisphenol A; CDC – Centers for Disease Control; EDD – Estimated Date of Delivery; EFW – Estimated Fetal Weight; ELEAT – Early Life Exposure Assessment Tool; ELGAN – Extremely Low Gestational Age Newborns; GA – Gestational Age; LGA – Large for Gestational Age; NCS – National Children's Study; NHANES – National Health and Nutrition Examination Survey; NICHD – Eunice Kennedy Shriver National Institute of Child Health and Human Development; nuMoM2b – Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-Be; PBDEs – Polybrominated Diphenyl Ethers; PCBs – polychlorinated biphenyls; PRAMS – Pregnancy Risk Assessment Monitoring System; SGA – Small for Gestational Age; SMFM – Society for Maternal-Fetal Medicine; SOGC – Society of Obstetricians and Gynecologists of Canada

Table 4

Essential and related measures in the PhenX Toolkit, which are relevant to the use of the new Pregnancy domain measures

	Essential measures		Related measures	
Pregnancy domain measure	**Measure**	**Domain**	**Measure**	**Domain**
Adequacy of Prenatal Care	Gestational Age	Pregnancy	Current Age	Demographics
			Current Pregnancy Status	Pregnancy
			Reproductive History	Reproductive Health
Concentrations of Flame Retardants	Current Age	Demographics	CBC	Rare Genetic Conditions
	Current Pregnancy Status	Pregnancy		
	Gestational Age	Pregnancy		
Concentrations of Phenols and Parabens	Current Age	Demographics	Home and Workplace Exposures to Floor and Wall Materials	Environmental Exposures
	Current Pregnancy Status	Pregnancy	Personal Care Products	Environmental Exposures
	Gestational Age	Pregnancy		
Concentrations of PCBs and Persistent Pesticides	Current Age	Demographics	CBC	Rare Genetic Conditions
	Current Pregnancy Status	Pregnancy		
	Gestational Age	Pregnancy		
Concentrations of Trace Metals	Current Age	Demographics	CBC	Rare Genetic Conditions
	Current Pregnancy Status	Pregnancy	Selenium	Nutritional and Dietary Supplements
	Gestational Age	Pregnancy		
Current Pregnancy Status	Current Age	Demographics	Reproductive History	Reproductive Health
	Gender	Demographics		
Difficulties in Pregnancy	Gender	Demographics	Prenatal and Postpartum Depression	Pregnancy
			Reproductive History	Reproductive Health
Family History of Pregnancy Complications	Current Age	Demographics	Causes and Treatments of Known Infertility	Reproductive Health
	Gender	Demographics	Contraceptive Methods	Reproductive Health
			Difficulty in Conceiving	Reproductive Health
			Family Health History	Rare Genetic Conditions
			Female Reproductive Organ Surgical Procedure	Reproductive Health
			Reproductive History	Reproductive Health
Gestational Age	Current Age	Demographics	Current Age	Demographics
			Pregnancy Status—Mother and Baby Health	Tobacco Regulatory Research
			Reproductive History	Reproductive Health
			Serial Pregnancy Weight Gain	Anthropometrics

	Essential measures		Related measures	
Pregnancy domain measure	**Measure**	**Domain**	**Measure**	**Domain**
			Total Pregnancy Weight Gain	Anthropometrics
			Birth Weight	Anthropometrics
Fetal Growth	Gestational Age	Demographics	Birth Weight	Anthropometrics
	Height	Anthropometrics	Pregnancy Status—Mother and Baby Health	Tobacco Regulatory Research
	Serial Pregnancy Weight Gain	Anthropometrics	Current Age	Demographics
	Race	Demographics	Total Pregnancy Weight Gain	Anthropometrics
	Ethnicity	Demographics		
	Reproductive History	Reproductive Health		
Gestational Diabetes	Current Pregnancy Status	Pregnancy	Family History of Diabetes	Diabetes
	Gender	Demographics	Fasting Plasma Glucose	Diabetes
			Fasting Serum Insulin	Diabetes
			Oral Glucose Tolerance Test	Diabetes
			Personal History of Type I and Type II Diabetes	Diabetes
			Reproductive History	Reproductive Health
			Serial Pregnancy Weight Gain	Anthropometrics
			Total Pregnancy Weight Gain	Anthropometrics
Health and Wellness Before, During, and After Pregnancy	Gender	Demographics	Body Mass Index	Anthropometrics/Substance Abuse and Addiction Collection
			Cigarette Smoking Status	Alcohol, Tobacco, and Other Substances
			Current Age	Demographics
			Current Quality of Life	Psychosocial
			Depression	Psychiatric
			Ethnicity	Demographics
			Gestational Diabetes	Pregnancy
			Height	Anthropometrics
			Weight	Anthropometrics
			Reproductive History	Reproductive Health
Mode of Conception	Gender	Demographics	Causes and Treatments of Known Infertility	Reproductive Health
			Contraceptive Methods	Reproductive Health
			Difficulty in Conceiving	Reproductive Health
			Reproductive History	Reproductive Health
Mode of Delivery	Gender	Demographics	Reproductive History	Reproductive Health

	Essential measures		Related measures	
Pregnancy domain measure	**Measure**	**Domain**	**Measure**	**Domain**
Prenatal and Postpartum Depression	Current Age	Demographics	Aggression and Hostility	Mental Health Research: Suicide Specialty Collection
	Current Marital Status	Demographics	Classification of Suicidal Ideation and Suicidal Behaviour	Mental Health Research: Suicide Specialty Collection
	Ethnicity	Demographics	Depression	Psychiatric
	Gender	Demographics	Hopelessness	Mental Health Research: Suicide Specialty Collection
	Race	Demographics	Impairment	Mental Health Research Core: Tier 1
			Insomnia	Mental Health Research: Suicide Specialty Collection
			Life Events	Social Environments
			Reproductive History	Reproductive Health

CBC – complete blood count; PCB – polychlorinated biphenyl